FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

GENERAL PLASTIC SURGERY DEVICES PANEL MEETING

(OPEN SESSION)

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Proceedings By:

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P R O C E E D I N G S [8:40 a.m.]

Agenda Item: Preliminary Business

DR. GANTT: I would like to get started. I do apologize for the delay. We had to set up the microphones somewhat differently.

Good morning everyone. We are now ready to begin this meeting of the General Plastic Surgery Devices Panel. I am Gail Gantt, the Executive Secretary of this panel, and a reviewer in the General Plastic Surgery Devices Branch.

I remind everyone that you are requested to sign in on the attendance sheets which are available at the tables by the doors, and you may also pick up an agenda, panel meeting roster, and information about today's meeting there. The information includes how to find out about future meeting dates through the Advisory Panel Phone Line and how to obtain meeting minutes or transcripts.

Before turning the meeting over to Dr. Morrow, I am required to read two statements into the record, the deputization of the temporary voting member statement and the conflict of interest statement.

This is the conflict of interest statement for the General and Plastic Surgery Devices Panel Meeting, May 5th, 1997. The following announcement addresses

conflict of interest issues associated with this meeting as made part of the record to preclude even the appearance of impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interest. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

Okay. We would like to note for the record that the agency looked into the consideration, took into consideration certain matters regarding Dr. Ricardo Azziz. Dr. Azziz reported that he and his institution have past interest in the product at issue and other related products. Since these were past involvements, there is no continuing financial interest and Dr. Azziz's role on the panel on the sponsor's study was limited to enrolling patients. The Agency has determined that he may participate in the panel's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Now, I will read the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27th, 1990, and amended April 20th, 1995, I appoint the following as voting members of the General and Plastic Surgery Devices Panel for the duration of the meeting on May 5th, 1997: Dr. Marian Deshmuck, Dr. Thomas Downs, Dr. Susan Galandiuk, and Dr. Barbara Levy.

For the record, these persons are special government employees and are consultants to this panel or consultants and voting members of another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the

material to be considered at this meeting and as designed by Dr. Bruce Burlington, Director for the Center for Devices and Radiologic Health.

Okay. At this time, I would like to introduce Dr. Monica Morrow, who is the Acting Chairperson for today's meeting.

Agenda Item: Introductions

DR. MORROW: Good morning. My name is Monica Morrow. I am Associate Professor of Surgery at Northwestern University Medical School, Director of the Lynn Sage Comprehensive Breast Program.

Today, the panel will be making recommendations to the Food and Drug Administration on a premarket approval application.

The next item of business will be to introduce the members of the panel and those of the FDA who are seated at this table. I would ask each person to please state their name, title, institution and your status on the panel, that is voting member, temporary voting member, consumer representative, et cetera. We will start on the far side, the far end with Dr. Dorfman.

DR. DORFMAN: Dr. Sally Faith Dorfman, Director of

the Division of Public Health and Education to the Medical Society of the State of New York, Consumer Representative.

DR. DOMECUS: I am Cindy Domecus, Senior Vice President of Clinical Research, Regulatory Affairs, and Quality Assurance for Conceptus. I am the Industry Rep. to the OBGYN Devices Panel. I am on loan to this panel today since the industry rep of this panel is involved in the sponsor presentation.

DR. GALANDIUK: Susan Galandiuk. I am Associate Professor of Surgery at the University of Louisville, and am a temporary voting member.

DR. DESHMUKH: I am Narayan Deshmukh. I am a General and Vascular Surgeon at the Guthrie Clinic, Sayre, Pennsylvania, and Clinical Associate for General Surgery at SUNY-Syracuse, and the Allegheny Campus. There is one correction. I am not an M.P.H. There is an error here. I do not have a Master's in Public Health.

DR. LEVY: I am Barbara Levy. I am an Assistant Clinical Professor of Obstetrics and Gynecology at the University of Washington, and a Clinical Gynecologist in the Federal Way, Washington area. I am a temporary voting member on the panel from the OBGYN Devices Panel.

DR. AZZIZ: I am Ricardo Azziz. I am Professor of

Obstetrics and Gynecology and Medicine at the University of Alabama at Birmingham, in Birmingham, Alabama. I am a temporary voting member.

DR. GANTT: I will reintroduce myself. I am Gail Gantt, the Executive Secretary of the Committee.

DR. DUNCAN: I am Titus Duncan. I am the Director of Endosurgery at Georgia Baptist Hospital in Atlanta, Georgia, and Assisting Clinical Professor of the Medical College at Georgia, in Augusta, Georgia, and I am a voting member.

DR. DOWNS: I am Tom Downs, Professor of Biometry, University of Texas School of Public Health at Houston. I am a temporary voting member here from the OBGYN Devices Panel.

DR. WITTEN: I am Celia Witten, the Division Director of the Division of General and Restorative Devices at the FDA.

DR. MORROW: I would like to note, for the record, that the voting members present constitute a quorum as required by 21 CFR Part 14.

With that, we will begin with Dr. Celia Witten, Director of the Division of General and Restorative Devices, and Steven Rhodes, from Plastic and Reconstructive Surgery

Branch, to present a division update.

Agenda Item: Division Report Updates - Tissue Initiative

DR. WITTEN: I would like to welcome the panel and everyone else who is participating today. We at the FDA appreciate the panel's participation in these meetings and your giving your expertise to us for these product reviews.

I want to update the panel today on a comprehensive regulatory framework for products derived from cells and tissues that has been proposed by the Center for Biologics, Evaluation and Research and announced on February 28th of this year. Although this was an initiative from the Center for Biologics, since regulation of some of the products this panel may see may be affected by this proposed rule, I will summarize briefly some of its highlights since I think it is of interest to this panel.

The proposed regulatory framework provides a tiered approach, with the level of regulation in proportion to the degree of risk of the product. In designing this approach, the FDA focused on five public health and regulatory questions and they are as follows: How the spread of communicable disease can be prevented, what processing controls are needed to prevent contamination and

preserve the integrity of cells and tissues, how clinical safety and effectiveness can be assessed, what labeling and promotion are appropriate for a given product, and how FDA can best monitor and communicate effectively with the cell and tissue industry.

For each of the above five questions that I have just listed, the FDA, in its proposed regulatory framework, will assess the level of concern. Just to give one example, infectious disease concerns would be greater for allogeneic tissues than for autologous tissues and this type of concern would be reflected in the proposed regulatory approach.

The regulatory scheme was discussed in an open public section on March 17th and the proposed rule is available on the Internet.

I would like to introduce now Steven Rhodes, who is the Branch Chief of the Plastic and Reconstructive Surgery Branch, who just performed a review of this product. Mr. Rhodes will provide an Update of the activities of this branch, as related to the last panel meeting and other activities of the branch.

Agenda Item: Update from November 1996 Panel Meeting

MR. RHODES: Thank you, Dr. Witten. Welcome to

the panel and welcome everyone.

I want to report on two activities in the Plastic and Reconstructive Surgery Devices Branch since the last panel meeting in November. The first, in that general meeting, the panel recommended approval for Tissue Sciences Dermograph TC, a temporary lung covering for severely burned patients.

In March of this year, FDA approved the product and also took the panel's recommendation that it be approved on the condition that the sponsor conduct post-approval studies on 200 additional patients for an infection risk.

The second thing I wanted to report on was in November there was a notice of recommendation published in the Federal Register for reclassification of Suction Lipoplasty Systems. The 90-day comment period ended in February and all of the comments that we received were favorable, in support of reclassifying Suction Lipoplasty Systems from a Class III, requiring a pre-market approval application, to a Class II, requiring a 510(k) special controls. The FDA is currently in the process of reviewing those comments.

With that, I am going to turn it back over to Dr. Morrow.

Agenda Item: Open Public Hearing

DR. MORROW: Thank you. The next portion of the meeting is the public comment, open public hearing. If there are any members of the audience who desire to address the panel, could you please come forward at this time. Speak into the mike, state your name, your affiliation and any financial interest you may have with the product under discussion.

[No response.]

DR. MORROW: Seeing none and having none listed, we will now proceed with the sponsor's presentation. I would like to remind public observers at this meeting that, while this portion of the meeting is open to public observation, public attendees may not participated except at the specific request of the panel.

Agenda Item: Sponsor Presentation - Genzyme Corporation - Product: Sepracoat

DR. BURNS: Thank you. Good morning, Dr. Morrow, and members of the Advisory Panel. I am Jim Burns, Vice President for Biomaterials and Surgical Products Research at Genzyme Corporation, and I will be making our introductions this morning and a review of our agenda.

Perhaps we could have the lights down just a

little bit. I would like to begin, on behalf of Genzyme, by thanking the Food and Drug Administration PMA Review Staff for their much hard work and deliberation during the review process. We welcome the opportunity to come before the panel today for consideration of our PMA application.

I would like to take a minute to go through our agenda and introduce our guests who will be presenting with us today. I am going to begin with an introduction to Sepracoat, a description of the product, how it works, and a brief summary of our preclinical testing.

That will be followed by some background information on adhesions and the clinical problem presented by Professor Harold Ellis. Professor Ellis is well-known in the area of surgical adhesions. He is perhaps the world's foremost expert over the last 30 years on this topic. He is an Emeritus Professor of Surgery at the University of London, and he is also currently a Clinical Anonymas at the United Medical and Dental Schools at Guy's Campus in London.

Over the last 30 years, as I mentioned, Professor Ellis has published extensively in wound healing for surgeons, the pathophysiology of adhesions, their incidence and clinical consequences.

Following Professor Ellis' presentation,

Dr. Michael Diamond will present our clinical trial results for Sepracoat. Dr. Diamond is Director of Reproductive Endocrinology and Professor of Obstetrics and Gynecology at Wayne State University School of Medicine.

Next, would be Dr. Richard Moscicki, who is our Chief Medical Officer at Genzyme. He will present some additional issues and analyses of our Sepracoat trials.

Dr. Robert Beart will present his view of Sepracoat, potential utility in intra-abdominal surgery. Professor Beart is Professor of Surgery, and Chairman of Colorectal Surgery at the University of Southern California School of Medicine. He is the former Editor-in-Chief of Diseases of the Colon and Rectum and he is an Editorial Board Member of Annals of Surgical Oncology, Journal of American College of Surgeons, and The Journal of Laparoscopic Surgery.

Then I will provide a brief summary statement.

The original concept of Sepracoat came from an observation that, for the most part, all surgeons really had available to them to prevent adhesions was good surgical technique. There was also no method available to them that would allow them to try to do that better, to try to limit the amount of tissue damage that could occur during surgery

by surgical technique that could then prevent adhesion formation.

Thirdly, that adhesions very often would form throughout the surgical field, even in areas outside of direct operative trauma.

Based on those observations, we designed Sepracoat coating solution to have the following design criteria: To protect tissues intra-operatively throughout the entire surgical field, to be safe, and something that is very, very easy to use during the surgical procedure.

Sepracoat is a 0.4 percent solution of sodium hyaluronate or HA, which is a high molecular weight glycocyamine of ligand that is ubiquitous throughout the extracellular matrix.

Sepracoat is applied to tissues intra-operatively at the very beginning and throughout the surgical procedure to provide a hydrophilic protective barrier to tissues during the surgical process, during surgical procedures. The intent here is to reduce the amount of tissue damage that can occur from desiccation or manipulative abrasion.

What it is doing is maintaining and perhaps enhancing, during the surgical procedure, the natural tendency of the tissue to be lubricous and not stick

together. It therefore reduces what w call de novo adhesion development.

I would like to point out that we have a bottle of Sepracoat -- this is our European package here of the Sepracoat. Sepracoat is marketed in Europe. So, I would like that to be passed around. If you can work the top open, you can actually feel it and do what you like with it, play with it.

So, I would like to describe what a de novo adhesion is because it is very important for understanding how Sepracoat was intended to actually work. There are two types of de novo adhesions, as defined by Diamond and Azot in 1993. The first type is an adhesion to sites that have no operative procedure and no pre-existing adhesions that existed at the time of the operative procedure.

Secondly, the second type is adhesions to sites that have no pre-existing adhesions and had no operative procedure.

In this case, this is a situation where you might use a barrier to prevent adhesions. In the first case, it is difficult to say where adhesions may form because of the tissue damage that could occur diffusely throughout the surgical field. Sepracoat is intended to prevent this type

of adhesion. So, when we talk about de novo adhesions today, we will be talking about de novo adhesions of this first type that are at sites outside the direct area of surgical trauma.

This diagram illustrates the cascade of events that can occur following a serosal injury. A serosal injury can occur because of abrasion, ischemia, desiccation, foreign body reaction. The ensuing inflammatory response is intended to allow normal remesotheliazation and generation of an intact serosa to occur. If the damage is too severe, this inflammatory response can lead to an adhesion. This is, again, where a barrier would be used where you know that where you have severely-traumatized tissue, you would place a barrier over that site to try to limit adhesions to that site.

Sepracoat acts at this stage. It coats the tissue and tries to minimize the extent or the amount of serosal trauma, therefore reduction the exuberance, if you will, of the inflammatory response to help allow normal remesotheliazation to occur.

That is illustrated in the following two slides histologically. This is an HNE stain of the Rat Cecum. This is a typical model that we use in much of our

preclinical research. This is two days after a standard amount of gauze abrasive force to the surface of the cecum that was precoated prior to abrasion with lactated Ringer's Solution. We see that there is hypertrophy of the serosa. There is influx of inflammatory cells, and you cannot see an intact mesothelial surface. This is typical of what happens with gauze abrasion in this model.

In contrast, if one is to coat that surface with Sepracoat prior to exposing the surface of the cecum to the exact same amount of abrasion force, we see histologically that it appears that there is less tissue damage. There are fewer inflammatory cells, there is less hypertrophy of the mesothelium. This is a situation which would be less likely to form adhesions.

That is shown on this slide here, which, if we take this rat cecum abrasion model and look seven days out, we see that, with no coating or a buffered saline solution applied to the cecum prior to abrasion, that approximately 10 percent of the animals have no adhesions.

As we increase the concentration of HA in this coating solution, we get more animals with no adhesions. Sepracoat is a 0.4 percent solution of HA. We can see that in this series that we have the maximal effect of these

three solutions with Sepracoat.

This slide illustrates the effectiveness of pre-coating versus post-coating. This is in a rat uterine horn laser thermal injury model by Irman and Gomelle. What Dr. Gomelle developed was a model for studying tissue injury and adhesions using a very standardized model of thermal injury.

In this model, if he exposes the horns to his laser injury and then adds buffered saline or an HA solution after the injury, we see that virtually 100 percent of the animals have adhesions to the uterine horn. If he pre-coats the uterine horn and then exposes it to buffered saline or -- I am sorry, pre-coats it with buffered saline and then exposes the horn to laser thermal injury, he sees a similar number of animals with adhesions. However, if he precoats the uterine horn with HA, which is represented by this bar, and then exposes to thermal injury, fewer animals have adhesions to the uterine horn.

We have conducted a number of preclinical efficacy studies of Sepracoat to more exactly define its mechanism of action. I will not go through all of the details of those studies, but I welcome questions during our question and answer period at the end of our presentation.

But I would like to point out that what we have found from these studies primarily using the rat cecal abrasion model is that not only is the HA concentration in Sepracoat important for adhesion prevention, but it is really the viscosity of the solution which imparts its adhesion prevention qualities.

This was supported in histological studies which I previously alluded to in which we showed that increasing concentrations of HA or the increasing viscosity of the HA solution gives superior tissue protection not only to gauze abrasion but also to desiccation.

We have conducted over 20 pre-clinical and non-clinical safety studies on Sepracoat. Again, I am not going to go through each and every one of these, but I would be happy to answer any questions that you may have specifically on any of these studies.

These studies have basically shown that, for Sepracoat's intended use as a pre-coating in intra-abdominal surgery, that it is safe, biocompatible and nontoxic. Again, I will be happy to answer questions about these during the question and answer period.

Well, in summary, Sepracoat has been shown to be a biocompatible, safe, and non-toxic substance based on

pre-clinical animal studies, that it acts to reduce de novo adhesion formation by limiting intra-operative tissue trauma and that the effectiveness of Sepracoat is related to the solution viscosity.

The next speaker will be Professor Ellis to talk about the clinical consequences.

DR. ELLIS: Good morning, ladies and gentlemen. My name is Harold Ellis, Emeritus Professor of Surgery, University of London. I have been retained as a consultant by Genzyme for this meeting. My fair was paid to Washington from London, but I have no other financial interests in the company.

I am here to discuss the clinical problems of intra-abdominal adhesions. The most important problem to the surgeon is as a common cause of intestinal obstruction. They also provide difficulties to the surgeon in re-exploring the abdomen that has been submitted to previous surgery. To the gynecologist it is an important cause of tubal obstruction, and, again, to the gynecologist, it may present as women with pelvic pain following surgery.

In the western world it is responsible for about one-third of all cases of intestinal obstruction of large and small bowel together. Since adhesion obstruction only

occurs in small bowel, when we exclude large bowel obstructions, due to cancer, diverticular disease, and so on, we have the quite amazing figure back in the western world of small bowel instruction is likely to be due to adhesions in anything from 65 to 75 percent of all cases.

So, a patient who appears in the accident and emergency department with an obvious small bowel obstruction, who has not got a strangulated external hernia, but who has got one or more scars on the abdomen, is almost certainly going to have intestinal obstruction due to post-operative adhesions.

At surgery, if it is an early case, such as this, it is a very easy procedure to divide those adhesions or that adhesion. Now, this adhesion might be directly at the site of previous surgery, i.e., it might be at the site, for example, of an anastomosis. It might be at the site of the abdominal scar, or it might be quite distant from the surgical procedure, a de novo adhesion or adhesions perhaps due to surgical gauze, perhaps due to the powder on the surgeon's gloves, perhaps due to the trauma of the general laparotomy performed by the surgeon.

So, within the first few hours, a relatively simple abdominal operation. Delayed the procedure

overnight. Eighteen hours later the bowel is now gangrenous and requires resection. The bowel may actual perforate. Now, of course, there is a very significant morbidity and, indeed, a significant mortality from this emergency.

Now, there are a lot of questions that need to be answered. How frequently do adhesions occur after abdominal surgery? How soon do adhesions produce obstruction? How often do they product obstruction? How much work do they represent to the surgeon? Are there any particular operations or particular risks? These represent questions after questions which clinicians ask and which I am sorry to say the standard textbooks do not provide very accurate answers.

However, our own observations have provided some answers to these questions. For example, at first-time surgery, about 10 percent of patients, in our own experience, have intra-abdominal adhesions. If you operate on a patient with gall stones and the gall bladder has got elemental adhesions to it for example. However, in patients who have had one or more previous operations, in our experience, some 94 percent have post-operative adhesions. Indeed, this is the experience of any surgeon who has taken the bother to document these cases.

So, for practical purposes -- let's just go back to that. For practical purposes, anybody with a scar on the abdomen has a very, very high chance of having intra-abdominal adhesions, especially if the previous surgery has been of a major character.

Now, of course, the vast majority of people are completely free of any problem following surgery. Ten or 15 years later, they will tell you that they have had no bother from their operation. However, a percentage will present with obstruction. Because abdominal surgery is so common, as I have already mentioned, these figures now become very significant.

I am afraid that one slide has slipped. That slide simply showed that in a very large series of cases that we followed up ourselves for over a year, one percent of our patients came back to our own service with intestinal obstruction within a year of operation requiring further surgery for intestinal obstruction due to adhesions. Of that one percent of cases, exactly a half of those, .5 percent, actually presented within the first four weeks of operation.

So, from our study and others, approximately one percent of all abdominal surgery will present with

intestinal obstruction within a year of surgery.

Now, in a series of 80 patients readmitted with intestinal obstruction due to adhesions, we were able to analyze how long the time from surgery. Not surprisingly, about 40 percent of our cases had their previous surgery within a year; in one to five years, another 20 percent; five to 10 years, another six percent. And then quite surprisingly, and this is perhaps something that surgeons are not aware of, 20 percent of our cases actually extracted 10 or more years following the initial surgery. So this is a lifetime risk. In our own study, our longest interval was 38 years from the original surgery to presenting with in fact a lethal intestinal obstruction due to adhesions.

Now, this, again, is an important subject. Having divided the adhesion and relieving the obstruction, the patient is at considerable risk of recurrence of intestinal obstruction. Any experienced surgeon will be well familiar with patients who had two, three, four, five, many reinterventions of adhesion obstruction.

Because it is a lifetime risk, naturally the percentage recurring varies widely with the length of follow-up and in published figures it varies from eight percent to 20 percent of patients presenting with recurrence

or recurrences of intestinal obstruction due to adhesions.

The workload in our own surgical unit, which was a general surgical unit, we found that intestinal obstruction due to adhesions accounted for three percent of all of our laparotomies and 29 percent of all of our obstructions. I would think that is fairly standard for the experience of most general surgeons.

So to sum up, adhesions occur almost invariably after major surgery. Most patients will go through life without any further problems. Within our own experience, one percent will develop adhesion obstruction within a year, half of them within a month. And then there is a lifetime risk of adhesive obstruction for the rest of that patient's life, constituting about one percent of all admissions to hospital, about three percent of all laparotomies in a general surgical unit at least in the United Kingdom. Thank you very much.

DR. DIAMOND: Good morning. My name is Michael Diamond. I am a paid consultant to Genzyme. In addition to the issues that Professor Ellis has just raised about the potential concerns of what post-operative adhesion development can cause, as a reproductive surgeon and as a gynecologist, I am also concerned about the potential

detrimental consequences of any post-operative adhesion development on the fertility as well as on the potential contributing cause to pelvic pain. This occurs even if it is just one adhesion that might develop.

Now, the clinical hypothesis for the clinical trial data that I am presenting today is that precoating with a hyaluronic base solution produces no adhesion formation at the locations of indirect surgical trauma. Pretreatment with Sepracoat is superior to the control pretreatments.

Now, this study was conducted by 17 different investigators. These are investigators actually from all over the United States and Canada.

The study designed that was employed was a multi-center, randomized mass placebo-controlled study. The protocol involved gynecologic procedures, deploying of laparotomies as the initial operative procedure. The patient subsequently would then have a second local laparoscopy to assess post-operative adhesion development.

At the time of the initial operation, the surgical procedures that are most commonly performed were myomectomies, tubal surgeries and ovarian surgeries. These were being done for individuals who wished to conceive. The

randomization for the study was the installation of either Sepracoat or a phosphate buffered saline, abbreviated PBS solution. This was done immediately prior to the initiation of the surgical procedure. The test solution was then applied, the initiation of the procedure ensues, the peritoneal was opened. It was then reapplied after irrigation or at least every 30 minutes throughout the operative procedure and then again at the conclusion of the procedure. After each of these installations, any residual solution that remained in the pelvis was removed.

The adhesion evaluation system that was utilized was an adhesion scoring system which has been previously described and published in the Utility of Sterility in 1994. This system utilizes 23 different sites throughout the abdominopelvic cavity, looking at them for the presence or absence of adhesions.

On the next slide, I will go into exactly what those sites were.

The primary end point that we were interested in is what is listed here, for instance, the mean proportion of available locations with any de novo adhesion formation resulting from indirect surgical trauma. Going back to what Dr. Burns talked about earlier, the indirect surgical

trauma. The specific type would be abdominal adhesions.

A second end point that we were interested in was the percentage of patients with at least one de novo adhesion resulting from any indirect surgical trauma.

This slide lists for you the 23 sites throughout the abdominal pelvic cavity that were looked at for the presence or absence of adhesions. What you can see is that there were many sites along the peritoneum, the abdominal wall, sites along the peritoneum and the pelvis, the reproductive organs, and then the small bowel, the large bowel and omentum.

Note that some of these sites, such as the small and large bowel, represent actually very large surface areas.

I will mention to you that the primary analysis that we wish to look at was that the proportion of available locations of any de novo adhesions. That is represented for you here on this slide by Y. The question then is where does this Y come from? I would like to walk you through that so that you are very clear.

The denominator for this proportion that you see on the right here is A, which is the total number of available locations for de novo adhesion formation. This is

calculated by taking, as you can see here, by taking the 23 sizes throughout the abdominopelvic cavity where we are looking for the presence or absence of adhesions, and subtracting from that the number of locations with adhesions at the time of the initial operation and additionally subtracting from that 23 the number of sites with direct surgical trauma.

So, A, the total number of available locations for de novo adhesion formation represents the initial 23 sites minus the sites with the existing adhesions, minus the sites that get directly operated on during the operation. This A then becomes the denominator of a proportion.

The numerator here represents the actual number of available locations which developed de novo adhesion formation. So this ratio, again, then is a proportion of the available locations we subsequently found the procedure to have developed de novo adhesion formation.

The statistical methodology that was utilized in this trial is based on efficacy analysis which was 1TF, which was prospectively described by Genzyme and by the FDA in the protocol. It was on an intent-to-treat approach that was utilized. And the specific types of analyses you can see here and they are also included for you in the packet

that you have in front of you.

Now, this slide lists the demographics for the patient populations. The numbers that you see at the top here for the PBS group and the separate group represent the number of evaluable patients at second laparoscopy who had the potential to form de novo adhesion formation.

What you can see is that the PBS group, which ended up being 108 subjects, and then the separate co-treated group, this was 107 subjects. What you can also see on this slide is that we can look at age, height, weight and body mass index. If you can look at the right-hand side, you can see that there were no significant differences for any of these parameters. In fact, if you look at the numbers, they are very, very equivalent.

This slide looks at four intra-operative parameters. The first of these is the number of patients with baseline adhesions. What you can see here is that with PBS pre-treated patients, there were an average of 4.5 sites that initially had existing adhesions. This compared to 3.2 in the Sepracoat-treated patients. This, in fact, did turn out to be statistically-significant.

The second line here looks at the locations that were available for de novo adhesion formation. The number

was 16.1 sites. Potentially they will develop adhesion formation in PBS-treated patients, as compared to 16.9 patients in the Sepracoat-treated patient. Importantly, you will see, if you look over to the right here, this difference was not significant.

The question is how does this come about? The answer to that is due to the number of sites with direct surgical trauma with the initial operation. In fact, as it turns out, the patients who were in the Sepracoat pre-treated group, ended up with more sites of direct surgical trauma at the time of initial operation than did the patients in the PBS group. Thus, if you add together the number of locations with baseline adhesions and sites of direct surgical trauma, the resulting available number of sites for de novo adhesion formation is in fact no different between these two study groups.

The third line here looks at the time of the second procedure, which was no different between the two groups. In the same way, the average drop in hematocrit from baseline in the immediate post-operative period was also not significantly different.

This slide looks at issue regarding to the test solution application. As you can see, there were no

significant differences in the amount of test solution that was applied, the number of applications or the rate of application in the test solution throughout the study.

There was a significant difference in the amount of solution removed after each installation when it was somebody who had the operative procedure, being 563 CC's in the PBS pretreated patients, and 500 CC's in the patients treated with Sepracoat.

This slide looks at the efficacy analysis for this study. The top line here is looking at the proportion that we were primarily interested in, the mean proportion of available locations with de novo adhesions.

What I first wanted to call your attention to is this number over here in the control patients. The mean proportion here is .295, in other words, 29.5 percent. This number is actually very similar to a number that we have reported in a paper back in 1987. We were also looking at patients undergoing infertility surgery. We found an incidence of de novo adhesions for about 31 percent.

Now, compared to this 29.5 percent of PBS patients, among those patients who were pre-treated with Sepracoat, the proportion is .236 or 23.6 percent, and this is significantly reduced, as you can see on the right-hand

side here, from the control patients.

Now, the second line on this slide is the percent of patients with at least one de novo adhesion. This was the secondary hypothesis. It is actually very supportive of the data that I have just shown you. In fact, it actually does come to approach significance. As you can see, among the PBS-treated patients, there were 95.4 percent of patients who had at least one de novo adhesion, and this compared to 88.8 percent in most patients who were treated with Sepracoat.

If you look at these numbers conversely in the PBS group, only 4.6 percent of patients did not have any de novo adhesion formation, and this compares to 11.2 percent in the patients who were treated with Sepracoat.

Could I have the overhead please?

I mentioned to you, as I was going through the demographics, that there were two for which there were significant differences. One of these was the number of locations with baseline adhesions, and the other was the amount of test solution that was applied.

In order to further evaluate these issues, we performed covariate analysis and, in fact, that covariate analysis, the test solution application was not significant.

However, we did find that a number of locations with baseline adhesions was a significant covariate and, consequently, we performed a covariate analysis with a recalculation of the adjusted mean proportions. My pointer has died. But you can see the adjusted mean proportions. You can see that the PBS group was .26 or 26 percent, as compared to .20 or 20 percent in the Sepracoat group patients.

An important thing, if you look at the right-hand side, is that even when you control for this covariate, you can still see that Sepracoat retained its efficacy in helping to reduce de novo adhesion formation.

Could you turn that off please?

The next thing I wanted to draw your attention to is the issue of safety of Sepracoat, as was reported in this pivotal clinical trial.

This slide lists the adverse events that occurred in over five percent of patients in either the Sepracoat group or the control group. It is important to note that some patients could -- it was possible for patients to have more than one adverse event so, therefore, the numbers can add up actually quite high.

Of 114 parameters for which were being assessed,

there were five parameters for which a significant difference was identified at the .05 level. Those five were identified for you more clearly in this slide. There was pain at unspecified location, abdominal pain, nausea, dizziness and pharyngitis.

I want to call your attention to the fact that, although these occurred more frequently in the Sepracoat-treated patients, the severity of these was though to be either mild or moderate in the vast majority of patients. Furthermore, looking at the far right-hand side of the relationship, the vast majority of them were thought by the surgeons not to be related to the test agent that had been applied.

This slide looks at the summary of the serious adverse events that were reported again for Sepracoat and the control patients in the study. What you can see is that there were only two that were thought to possibly be related to what turned out to be the Sepracoat-treatment and there was one that was thought to possibly be related to what turned out to be the PBS treatment.

To summarize then Sepracoat reduced importantly the incidence or available locations of any de novo adhesions by 20 percent as compared to the control group.

Secondly, it reduced the incidence of patients with at least one de novo adhesion by seven percent.

Despite the fact that there were some minor statistical differences with regard to safety, these were thought to be mild or moderate in severity and usually were thought to be unrelated. Therefore, I think it is fair to conclude that the safety profile for Sepracoat patients was nearly identical to that of the control patients.

In conclusion, therefore, as a tissue precoating, Sepracoat has been shown in this randomized placebo-controlled mass study to be safe and efficacious in the reduction of de novo adhesion formations in locations of indirect surgical trauma.

DR. MOSCICKI: I would like to present some brief issues and analysis that I would like the panel to consider and perhaps add some additional perspective for your deliberation today.

A brief comment regarding the end points that were used. Dr. Diamond just told you that the primary interest was to look at the incidence of adhesions. The initial proposal to measure this incidence was to utilize a proportion of the available anatomic locations within the abdominopelvic cavity which would have any, that is one or

more, de novo adhesions. Consistent with a finding that Dr. Diamond had in a previous study, we would expect that this would be in the control group approximately 30 percent, similar to what was actually observed, if you note, in the study.

We then added a second measure which we thought would be extremely interesting, and that would be to look at this percent of patients with at least one de novo adhesion at any of the sites.

Now, this latter end point I would point out requires a remarkable degree of efficacy in order to achieve success. For example, there would be 23 possible chances that could be present to have even one adhesion, making the odds relatively low for success with this second interesting end point.

The first major point that I would like to address regarding the analyses is the use of the one-tailed test. As Dr. Diamond pointed out to you, the clinical hypothesis that was to be tested here was that Sepracoat would be superior to the placebo control. It is not interesting to have a product, of course, which is equal to a placebo control. So, therefore, we wished to prove the alternative hypothesis that Sepracoat is better than control and,

therefore, reject a null hypothesis that Sepracoat is equal or worse than the control.

The suitable and appropriate test for this is, in fact, one tail. So, the initial study design and sample size calculations utilized a one-tailed analysis. This is consistent with the FDA guideline and, furthermore was agreed to in previous communications prior to the analysis with the FDA.

Now, secondly, I would like to point out that in the analysis, the standard study is done to undertake a look for confounding factors. Among those in the analysis of variance, there was a statistically-significant treatment by investigator site interaction identified.

Now, what does this mean? This suggests that there is a variability in the treatment response observed at the different investigator sites. It turns out that one known anomalous investigator site was largely responsible for this interaction, site number three.

Prior to the analysis being conducted, we had known that this investigator had missed the initial and, in fact, several other essential training programs related to adhesion scoring. Approximately midway to three-quarters of the way through the trial, the monitor had identified that

there was evidence for disparity in this investigator's scoring and that the investigator was not following the protocol for scoring and attempted to correct this with the investigator. So it was no surprise to us when we were able to then identify that this did in fact turn out to produce an anomaly. In fact, removal of this anomalous site then makes the interaction insignificant.

As you can see here, this represents a statistical model looking at the effect of a site or investigator site. As you can see, after removal of site number three, this interaction that was present becomes insignificant. However, even if one uses this model to adjust for the site interaction, you can see that the result continues to be statistically-significant for the proportion end point. In fact, the exclusion of site number three produces an even more robust result.

If one does not adjust for this and uses -- goes back to the original analysis, then you can see that the exclusion of site number three also produces an increased difference, in which the mean percent reduction now increases to 30 percent and, once again, the T-value becomes far more robust.

If we looked at the second end point, in terms of

the patients with de novo adhesions, then, once again, we see a more robust effect which occurs by excluding the anomalous site, moving from a P value which approaches statistical significance to, in fact, one that achieves statistical significance if you use .05 as that measure.

I would like to go next to the overheads for just a moment. Again, in the submission of a PMA, it is customary to perform an integrated summary of safety data. This includes data from all of the clinical studies that were performed with the product. So this is taken directly from the PMA submission itself.

What is represented here in the Sepracoat group are the results of patients treated with forms of Sepracoat, including those which were of lower concentration and of lower viscosity and were present also not just from the pivotal trial, but also from a phase one safety trial in gynecologic surgery, a similar safety trial in abdominal surgery, and two cardiac surgery safety trials, one in adults and one in pediatric patients. The controls include not just placebo patients, but also non-treatment.

What is listed on this overhead for you are, I think, the five different adverse events that Dr. Diamond pointed out to you turned out to be statistically different,

although common to both control and Sepracoat in the pivotal trial.

Once again, I will point out that there were over 114 analyses performed. If one uses the statistical significance of .05, one might expect to find perhaps one out of 20 will turn out to be by chance alone to achieve that .05 level. However, when you look at the integrated safety data, I think that it is interesting to note that there is in fact no difference now among these between the control group and the Sepracoat group.

Now, because abdominal pain would be of concern to us and it may not be fair to include in this analysis patients who had received Sepracoat in the thoracic cavity, we also analyzed this removing those patients who had participated in the cardiac surgery trials.

Again, that is illustrated here in this overhead where, once again, despite removing these but including the other patients where there has been peritoneal exposure to Sepracoat, we, again, see that there is no statistical significance in the difference between the occurrence of these in the control and the Sepracoat group.

So, in conclusion, I think we can say that Sepracoat, again, significantly reduced the proportion of

locations within the abdomen (sic) that had any de novo adhesion by 20 percent. This, by a variety of different analyses, continues to show a statistically-significant result.

This is supported by an increase in the percentage of patients, as Dr. Diamond told you, who were, in fact, free of de novo adhesions. This difference was greater than two-fold, as he had pointed out to you.

This, at least, performs a positive effect and trend and, in some circumstances, under some analyses, it is even statistically-significant.

I think that the integrated summary data also supports the fact that Sepracoat had an acceptable safety profile.

Finally, I think that these conclusions are supported by multiple analyses which we have performed demonstrating the consistency of the results. Thank you.

DR. BEART: Dr. Morrow, panel members and guests, I appreciate the opportunity to share with you some thoughts about our experience with adhesions. Like Professor Ellis, I have no financial connection with this organization, other than those expenses involved with this trip.

We have heard some statistics from Professor Ellis

about the problems associated with intra-abdominal adhesions. In order to put that into some perspective with the denominator, we recently completed the study in Los Angeles County looking at the number of patients in this country (sic) that had intra-abdominal surgery during their lifetime. Based on an autopsy study in Los Angeles County, 43 percent of individuals in this country (sic) over their lifetime will have an intra-abdominal surgery.

Our experience with adhesions had been diffused and, like the general surgeons on the panel, I spent a fair amount of my time dealing with this issue. However, we have a unique model which I think gives even further insight into this problem. The ileo-anal procedure is one of the few and perhaps the only intra-abdominal procedure that is performed in an absolutely standardized way in a routine interval. And then at a specified interval that patient is re-explored with the opportunity to evaluate that patient for adhesive problems. Also, clinically, these patients are managed in a standardized way which allows one to evaluate the clinical significance, that is bowel obstructions, following surgery.

In multiple studies looking at this, the incidence of bowel obstruction clinically significant ranges between 20 and 40 percent. In our own institution, in the Francois

Study, it was actually 17.5 percent. At the University of Minnesota, it was actually 40 percent. So, we see a high incidence of clinically-significant bowel obstructions following this procedure.

In addition, when it comes time to close the ileostomy some six weeks later, 20 percent of patients have diffuse intra-abdominal or the so-called de novo adhesion referred to earlier which prevents standard peristomal incisions for closure of the ileostomy but, instead, mandates an intra-abdominal exploration through a midline incision.

Therefore, we see adhesions in the early period and in the late period, and they have a significant morbidity and in fact even mortality as Lancaster has shown, a five percent mortality related to abdominal adhesion. Therefore, intra-abdominal adhesions are a significant problem and they occur with a significant frequency to cause concern among general surgeons who are dealing with these patients on a daily basis.

These adhesions are not only in the area of direct injury, but they are remote, as I pointed out, in the ileo-anal model in at least 20 percent of patients.

As surgeons, we have tried through the years a

number of different mechanisms to try to prevent these. I have some of them listed here. None of these have proven to be routinely effective, particularly for the de novo or diffuse adhesion, a strategy which is not addressed by most of these products.

We have also attempted to allow the adhesions to form and to merely manage their formation in a way that minimizes their clinical consequences. That similarly has not been an effective long-term strategy.

I also would like to take this opportunity to point out that I think it is our impression that there is a substantive variation amongst patients which allows statistical evaluation of this problem to be difficult over the long-term and to analyze these patients effectively.

So we need a strategy which will prevent adhesions. I might also point out that when adhesions occur they recur frequently after treatment, even after surgery. They are clinically-significant in any where from 20 to 40 percent, again, in the Menses (sic) article, at 21 percent clinical return rate. These result in prolonged hospitalization.

This strategy, therefore, needs to be not only directed at the local adhesion where it forms or may form as

a result of direct trauma, but also at the diffused abdomen which is exposed throughout the surgical intervention and, therefore, remains a candidate for trauma throughout the abdomen.

The benefits of a product which have been shown to reduce de novo adhesions by 20 percent cannot be, therefore, understated. It would add significantly to our strategy to deal with adhesion disease. It is the only product that we are aware of that can reduce these adhesions or has been shown to be effective even though it is not 100 percent. I think we consider, in the face of the large numbers involved, a 20 percent reduction certainly to be significant.

I think, whenever we are looking at benefits, we also cannot ignore the risk side of the equation. When looking at these risks, in particular, the associated problems which were discussed in the last talk, I think they are those which we would commonly expect with intra-abdominal surgery. And certainly one would say that, one, they are not increased in their incidence and that they are relatively minor particularly when compared to the potential benefits of minimizing adhesions.

In my own mind, I could not identify a causal

relationship between pharyngitis, for instance, and the use of this product. That does not exclude the possibility, but I wanted to make the statement that I could not identify a causal relationship.

In summary then, I think the effectiveness of this product has been demonstrated as real and it offers a potential utility which we in the general surgical field would welcome. Any adhesion can have a clinical significance. The importance of these de novo adhesions is becoming increasingly clear as we have models such as I have discussed.

There is currently no product available to address this problem, and we think that this favorable risk-benefit ratio will be meaningful. Thank you.

DR. BEART: I would like to provide a brief summary of the previous discussion and presentation of our clinical trials within the perspective of the Code of the Federal Register for valid scientific evidence for conducting efficacy and safety studies in determining the approvability of medical devices.

I think, if you look at the CFR for valid scientific evidence, the most important thing is obviously that you have to have a well-controlled pivotal clinical

trial. We feel that the design of the Sepracoat trial meets this criteria. It was randomized, masked, and placebo-controlled, and it was conducted at 17 different -- or 23 different institutions but 17 different investigators were involved with the study.

Additionally, Sepracoat was shown to be effective in a pivotal efficacy study in gynecologic surgery that looked at not only pelvic structures, but also abdominal structures. This study looked at more anatomical sites than any other previous trial. We have conservative use of the product. Clearly, the effectiveness and mechanism of action of Sepracoat is supported by nonclinical studies.

Sepracoat is a 0.4 percent solution which was significantly shown to reduce the proportion of any de novo adhesion by 20 percent. This was statistically significant, even if the analysis was adjusted for covariate or for treatment by site interaction. This effectiveness was supported by the number of patients who had a reduction in any adhesion which was seven percent or conversely approximately two and a half percent fold increase in the number of patients with no adhesions.

Also, very importantly, we have established that Sepracoat is safe for its intended use as a pre-coating in

the intra-abdominal cavity. It has been applied to over 300 patients. Actually, I think that the number is 334 patients. This was in two abdominopelvic safety studies, as well as one pivotal gynecologic study. Again, this included high viscosity as well as low-viscosity solutions. Additionally, the safety of the product is clearly supported by the numerous pre-clinical studies that we have conducted in animals.

Based on the studies that we have conducted with Sepracoat, we have proposed the following indication, which is in the labeling which I believe that you should have in your package of information. Sepracoat coating solution is a bioresorbable tissue-protective barrier for prophylactic application at the beginning and throughout abdominal and pelvic surgical procedures to reduce the incidence of newly-formed adhesions resulting from incidental tissue damage.

That concludes our presentation this morning. We would be happy to take questions and answers at this time.

Agenda Item: Questions and Answers

DR. MORROW: Thank you.

The sponsor's presentation is now open for questions from panel members. Dr. Galandiuk.

DR. GALANDIUK: Has there been any data on the

effect of using Sepracoat in cases of intra-abdominal infection or having an infection occur post-operatively in a patient who has received this?

DR. BURNS: Actually, if I can take a moment before we answer that question to introduce the principal investigators that we have joining us today as well who can also answer questions specifically if they have to do with the clinical trials. Then, if we can, we will come back to answer your question.

We have joining us today Dr. Eric Beaver, who is Director of Reproductive Endoscopy at the Prisker School of Medicine at the University of Chicago, Dr. Karen Bradshaw, who is the Strauss Distinguished Professor of Women's Health and Associate Professor of Obstetrics and Gynecology and Surgery at the University of Texas Southwestern, Dr. Steven Schwaitzberg, who is Associate Professor of Surgery and Medical Director for the Center of Minimally-invasive Surgery at Tufts New England Medical Center in Boston, and Dr. Caylan Silverberg, who is an infertility surgeon in private practice, as well as a clinical assistant professor of obstetrics and gynecology at the University of Texas, San Antonio.

In addition to our PIs, who are in attendance

today, also with us is Dr. Richard Ciacchierini, who is a statistical consultant at C.L. McIntosh, and former Director of the Division of Biometric Sciences at the Food and Drug Administration, and Dr. Gene Goldberg. Professor Goldberg is in the Material, Science, and Biomedical Engineering Department at the University of Florida, and first pioneered the use of tissue protective solutions to be used in surgery to limit tissue damage and prevent adhesions.

So your question was -- perhaps you could restate it -- it had to do with the use of the product in the presence of sepsis or bacterial spillage?

DR. GALANDIUK: Well, adhesions are one of the ways that the organism will try to confine infection and preventing adhesions or minimizing them could theoretically predispose to more infection.

DR. BURNS: We have not actually looked at that issue specifically in any animal studies or any clinical trials. I actually might ask one of our experts to comment on that. I think what you are potentially asking is whether you might actually prevent the "good adhesions" that might form versus the adhesions that potentially could be problematic.

If I may, I will ask Dr. Ellis if he would not

mind coming to the table and addressing that question.

DR. ELLIS: Thank you very much. Certainly in other trials that have been carried out in prevention of adhesions, the very severe stimulus produced say by a gangrenous tissue, leading, anastomosis, serious sepsis, the methods that have been used, such as using topical plasmigen activator, and so on have been ineffective in the presence of a formidable stimulus to adhesion formation. So, just on theoretical grounds, I doubt if it would occur in this case.

DR. MORROW: Professor Ellis, before you leave, could you tell us, is there any data that says what percent of adhesive obstructions are due to adhesions to the wound site and the prior surgical site versus those that are due to de novo adhesions?

DR. ELLIS: No. I have not got any of those figures myself. We did not look for it. I am ashamed to say that we did not look specifically at that particular problem. Certainly, one's impression is that a good number, perhaps the majority, let's say, as a guess, 60-70 percent are to the laparotomy wound or to the actual operative site. But every surgeon, of course, is very well familiar with the abdomen, which is stuck from one end to the other with diffused adhesions. Perhaps that is an even more serious

problem. There, again, we believe that those adhesions result from diffuse injury, such as from laparotomy, gauze from glove powder, from suture material and so on.

It is an important point that should be looked into. But, as you have noticed, I am an emeritus professor, so I cannot do it.

DR. MOSCICKI: Dr. Morrow, I might add to your question. Again, we saw about 95 percent of these patients in this study in the pivotal trial did have adhesions related to indirect trauma, although that does not tell you how many of them also have them due to direct trauma.

However, we did look at some of these sites in an additional analysis looking at whether or not there had been an effect of Sepracoat on direct trauma. In that analysis, we saw that approximately 50 percent of the sites that had been exposed to direct trauma had adhesions as a result but did not have baseline adhesions previous to that site. To some degree I think that is interesting because it points out a potential specificity of effect related to the mechanism of action for the product. And we saw no effect then in this 50 percent occurrence related to direct trauma, whereas, we did in those related to indirect trauma.

Dr. Steve Schwaitzberg is also here who has

conducted some studies related to the infection potentially. Perhaps Dr. Schwaitzberg can answer the first question.

DR. SCHWAITZBERG: My name is Steve Schwaitzberg. I have no personal financial interest in this product, but we have performed independent clinical and preclinical investigations dating back to the 1980s.

In a capacity as a device evaluator in our research lab for almost 10 years, I was faced with the possibility of being among the first people in the United States to actually pour a hyaluronic-based solution -- hyaluronic acid solutions into the abdomen. One of my concerns was infection. We performed pre-clinical studies looking at the infection potential of HA solutions against a variety of different bacteria, both in vivo and in vitro and could find no increased risk of infection potential in that setting.

DR. MORROW: Are there other questions from panel members?

DR. LEVY: I have a question about the study design. Was there standardization across the centers or across procedures as far as packing, retractors, any kind of surgical technique? Then I have a second question about how direct trauma was defined.

For example, if there was surgery on an ovary, was the tube adjacent to that ovary considered a direct surgical trauma site or not?

DR. MOSCICKI: I will ask Dr. Diamond to address that since he was intimately involved with that design.

DR. DIAMOND: With regard to your latter question, as I understood it, you are asking if the ovary was operated upon is that a sign of direct surgical trauma? The answer to that would be yes.

DR. LEVY: My question is, if you were operating on the ovary on the right side, would we consider the tube on the right side a site of direct surgical trauma or not?

DR. DIAMOND: If the surgery on the right ovary was for a cyst, for example, where there was no involvement of the right tube, then any adhesion identified with a second procedure that involved the right tube would be a de novo adhesion. If the surgery on the right ovary initially was an adhesion from the right ovary to the right tube, then both would be a site of direct surgical trauma.

DR. MORROW: Could I expand on that for one second? If you had to lyse any adhesion to the small bowel, as part of the procedure, did that mean that the small bowel was then excluded as a site of de novo adhesion formation?

DR. DIAMOND: Yes. In fact, that is a very important point for the analysis of the data. Any adhesion to or any procedure on any site, adhesion of or procedure on any site excluded that as a site of adhesion, a site of de novo information. So what that means is that by reduction of the number of sites for de novo adhesion formation, that potentially is more than one adhesion that could develop to that site at the time of the second procedure the prevention of any adhesions developing to those sites. It looks like I confused you more than I answered your question.

DR. MORROW: Could you say that again please?

DR. DIAMOND: Yes. We had 23 different sites throughout the abdominopelvic cavity that were being evaluated. Any adhesion to any one of those sites or any surgery on any one of those sites would mean that that site could not be a location for de novo adhesion formation. The important part of that then is when you talk about how much reduction of adhesions, de novo adhesions that occurred, we are talking about the number of sites, the reduction of sites with de novo adhesions, not reductions in the number of adhesions.

DR. MORROW: Right.

Dr. Downs, did you have a question?

DR. DOWNS: Yes. I estimate from reading the materials that perhaps there were 80 PBS controls in stage one of the study and no .4 percent high viscosity HAs. In the second stage of the study there were 40 PBS controls and 120 .4 percent high viscosity HA-treated. In that sense, it is possible that the original first-stage 80 controls could be considered historical rather than concurrent controls. I wondered if any comparison has been made between the first 80 and the last 40 controls?

DR. MOSCICKI: I will turn to our statisticians who conducted that. Heather, would you like to answer that?

DR. KELLY: I am Heather Kelly. I was the statistician and Genzyme. Yes, we did look at that. It is not formally submitted in the PMA, but we did not see any differences. If you would like that information, I could get it for you after lunch.

DR. MORROW: I think we may have missed the first part of Dr. Levy's question.

DR. WITTEN: Excuse me. That material would need to be submitted for review. It is not something to provide after lunch at this meeting.

DR. KELLY: Okay.

DR. MORROW: About standardization of operative

technique, packing and so on, if maybe you could address that?

DR. DIAMOND: Sorry. There were a series of four different investigator meetings where we tried to go over with the participating surgeons exactly the protocols that we would want to have followed to try to assume -- to make the protocols that were being followed outside as similar as possible. But some of the specific things you talked about, like the manner in which the bowel was packed, were not one of the things that was specifically standardized, but would be consistent within that site with the surgeons.

DR. LEVY: Were the surgeons -- a lot of these are teaching institutions -- were the principal investigators the primary surgeons in all of these cases?

DR. DIAMOND: Either the principal investigators or their associates who, again, were trained in these sessions, as well as in sessions by the monitors at the individual hospitals, yes.

DR. MORROW: Dr. Azziz.

DR. AZZIZ: I have two questions. One of them is one that you earlier addressed which was the one-tail versus two-tail. I know of very few biological events that follow a one-tailed analysis. Although apparently that was agreed

on by FDA, you are looking at an agent which may actually make adhesions much worse. For the panel to determine that, you need to have a two-tailed test. So, I perhaps am unclear as to why the one-tailed test was chosen in the first place. Perhaps you can elaborate on that.

The second question is about masking and blindness. Were the videotapes that were taken during the surgeries, were they evaluated in any way and used? I know there were some problems with some of the quality of the videotapes. But I would surmise that a good 80-90 percent of the videotapes would have been viewable. So perhaps if we could address those two?

DR. MOSCICKI: In terms of the one-tailed test, I think we have pointed out our rationale for why we thought it was appropriate. That was supported by the statistical consultations that we had received. I would ask one of our statistical consultants, Dr. Ciacchierini, perhaps to address the appropriateness of the one-tailed test in this setting as well.

I also will then ask Dr. Diamond to address the videotape since he was responsible for the review of those videotapes. I know that Dr. Ciacchierini also performed some statistical analyses related to those that might be

pertinent to your question.

DR. CHIACCHIERINI: With regard to the on-tailed versus the two-tailed test, the one-tailed test is traditionally used when the interest of the persons doing the research involve just the either betterment or worsening of the condition. The concern about worsening -- the one-tail can be applied in either direction.

The hypothesis of a one-tailed test for the purposes of Genzyme was that they wanted to demonstrate that their product was superior to the control. Anyone could certainly have performed the exact same test to determine whether or not the Genzyme product was worse than the control and still use the one-tail criteria, which would be a more severe test than using the two-tailed criteria. So, I think that the determination of using a two-tailed test is a severe penalty on the manufacturer because it requires a level of evidence that may not be necessary when in fact the true nature of marketing the product, the product will only be marketed if, in fact, it is superior to the PBS control.

Now, with regard to the utilization of the video results, the initial protocol had never intended to use the video results. The video results were nonspecific in nature because there was a lot that was not seen on them. They

were extremely long in the sense that the person evaluating them sometimes had to look at them for up to two and a half to three hours. Therefore, the ability to visualize all sites was an extremely difficult situation.

At the request of the FDA, however, the company wanted to demonstrate that or wanted to test whether or not the onsite surgeon's evaluation was in any way bias relative to the determination of adhesions. In fact, this was done by performing what we know as McNamara's test to determine whether or not the discordances between the video reviewer and the onsite surgeon favored the adhesion admission of either the onsite surgeon or the video reviewer. And, in fact, for most of the site's visualized, there was an apparent pattern. In fact, for nine sites, there was a statistically-significant difference in the surgeon's calling more adhesions than the video control.

However, that only impacts the treatment if, in fact, there is a bias relative to the treatment, and that is, if the surgeon's called in favor of the .4 percent solution more frequently than they did the control. We performed that test, the test of homogeneity of those discordant pairs, by using a method recommended by Breslow and Day and, in fact, that did not demonstrate any

statistically-significant difference except in a couple of minor concerns.

We also did this for study site and we just confirmed the study site differences that were demonstrated on the analysis.

DR. AZZIZ: Then perhaps I am unclear as to how it was blinded if there was not an intention initially to have a blinded reviewer review the adhesion score.

DR. DIAMOND: The original protocol called for review by the surgeon as an assessment of efficacy. The surgeon did not know whether the solution that they would be utilizing was the test solution or Sepracoat. While they may have had some ideas, most of them have said they were not sure they could differentiate between which was the test solution. So when they would do their subsequent second look and assess for efficacy, they did not know to which group the patient had been assigned.

DR. MORROW: Before you leave, the original study on which you base this method of adhesion scoring, is there any data from that study about variability, reproducibility and that sort of thing?

DR. DIAMOND: By variability, reproducibility --

DR. MORROW: Like inter-observer variability on

the same patient.

DR. DIAMOND: The adhesion scoring system that we utilized, which was the fertility paper in 1994, actually the whole basis for that paper is comparing the viewpoints of 13 different surgeons viewing exactly the same videotape to see how often they called the same adhesions. We compared it not only with this scoring system that we utilized here, but also what is the American Fertility Society, and now the American Society for Reproductive Medicine Adhesion Scoring System, which looks at a fewer number of sites, for sites much more localized in the pelvis. What we found was that with the scoring system that we utilized here, we had a much higher, in fact, a significantly higher correlation between observers utilizing this scoring system than between the scoring system that had been previously proposed by the American Society of Reproductive Medicine.

DR. MORROW: And what was the correlation?

DR. DIAMOND: The correlations were up to about .7 -- actually I have a copy here that I could share with you if you would like.

DR. AZZIZ: Mike, I am sorry. If I could ask a question? About that, the paper that you published or that

was based on videotape reviews, as you said, of 13 surgeons doing videotape reviews; is that correct?

DR. DIAMOND: They were the same videotapes that were reviewed by the 13 different surgeons, correct.

DR. AZZIZ: Thirteen different surgeons. And that is based on videotape? I mean, the scoring system is based on a video review. Certainly, video reviews, no mater how good they are, are certainly very different than tangible palpation of an adhesion. So I am still, again, unclear. If the scoring system was initially designed based on the video review, why wasn't a video review included in the initial design of the study?

DR. DIAMOND: I think they are two different issues. The adhesion scoring system that was utilized in the manuscript -- first of all, specifically, we took videos where I felt that all of the sites that we wanted to look at, all 23 sites were visible. So we specifically selected videos which were good videos where all of the sites were identified so there was not going to be a problem of not seeing some of the sites which was a problem with the clinical trial. I was the blind reviewer. I can tell you that there were many videotapes, in fact, most of the videotapes, where you either could not see the entire

procedure -- at that point people were shutting off the video at different parts throughout the procedure, or you would not be oriented well, you would not know necessarily if it was a close-up view, whether you were getting into the anterior cul-de-sac or the posterior cul-de-sac. Or you would see some fat and you would not know whether it was omentum or appendices epliplica, or you would see an adhesion going to a left ovary, but you could not tell for sure what it was coming from. This is because it is a close field of view. If you do not have the advantage of a tactile sensation sometimes, if you have an ovary adherent to the lateral side and you put a probe behind and lift it up, you sometimes get a tactile sensation that there is an adhesion there. Whereas, if you are a video reviewer, unless you see it jump up all of a sudden, you are not always going to be able to differentiate that.

So I think that there is a difference in reviewing the videos that were part of the surgical protocol where they weren't as high-quality videos and they were not specifically selected for the purpose of trying to do inter-individual comparisons, which was the case with the manuscript.

DR. AZZIZ: I understand that. I am sorry. No.

What I am simply asking is the scoring system in the variability that Dr. Morrow asked is based on video review. The question is, if you chose that system to follow for adhesion scoring, then that was based on video reviews, which would mean that either you would have no variability data based on adhesion scorings in vivo or it should have included video recording from day one. That what I am trying -- I am not obviously arguing with a way that the videotapes were faulty. It is the issue that your adhesion scoring, in answer to Dr. Morrow's question, was based on video reviews. Am I incorrect on that?

DR. DIAMOND: The adhesion scoring for the manuscript was based on video review, correct. The adhesion scoring for this protocol was primarily -- the primary way that that was done was by the surgeons at the time of surgery itself. As you just year, subsequently going back and looking at the data that I was able to generate from the videos that we are seeing, there does not appear to be any bias on the part of the surgeons favoring the treatment group as compared to the control group.

DR. AZZIZ: But we do not have any variability data with in vivo adhesion scoring?

DR. DIAMOND: You are talking about do we have --

we do have data which looks at what the original surgeon reported and what I have reported as the blind reviewer. Yes, we do have that data, if that is what you are asking.

DR. AZZIZ: No, but that is okay.

DR. MORROW: Are there further questions from the panel?

DR. DOWNS: I would like the company's reaction to this. If I knew that a patient underwent surgery in stage two and I can guess whether that patient was in the treated or the control group and be right 75 percent of the time just by always saying that they are in the treated group -- if I know that a patient is in stage one I can guess that the patient's treatment or control status and be right 100 percent of the time by always calling them in the control studies or control group.

DR. DIAMOND: If you knew what the block randomization was, then the assumptions you just made were correct. But, in fact, the surgeons at the time they were participating in this study did not know what the blocks were.

DR. GALANDIUK: I had a question on how well the surgeons knew what they were using even though there is less tactile sensation. With gloves on the Sepracoat feels like

silicone, whereas, the buffered saline would feel like water.

DR. DIAMOND: I think that is probably a question that might be better for one of the surgeons who actually participated in the study to answer as opposed to myself, having been a reviewer.

DR. MOSCICKI: Yes. I would like to ask Dr. Kalan Silverberg to answer that, as well as perhaps Dr. Schwaitzberg.

DR. SILVERBERG: I am Kalan Silverberg. I have no financial association. I really disagree with that. I do not think that you can really tell. I think that, if you have got your two products sitting side-by-side and you are assessing it then, you may be able to feel a difference. But intra-operatively we were unable to. We had no idea we were blinded.

DR. MOSCICKI: I will just point out again that Dr. Silverberg did participate in the trial and was handling the material. Dr. Schwaitzberg also had participated in the abdominal safety trial.

DR. SCHWAITZBERG: This is Steve Schwaitzberg. While you may be able to get some inferences in the higher viscosity solutions, the general conduct of a busy surgical

practice and most of the investigators are quite busy trying to reevaluate patients six weeks later. It is almost impossible to remember what people got. I mean, for those people who are engaged in the practice of surgery, we are constantly referring back to our notes for operations that we have done within the past year to be certain that when it comes down to a clear and colorless solution that was given several weeks before. At the time of the evaluation, nobody really could remember with enough certainty to introduce any bias.

DR. MOSCICKI: And I think that that lack of bias was supported by careful statistical analysis that Dr. Chiacchierini had performed.

DR. SILVERBERG: If I could just add one more thing? That really cannot be overstated. We made no notation or no remarks at the time of the initial surgery as to what our impression was. I guess you could say, well, gee, we had a 50/50 likelihood of guessing correctly if we would have guessed at that time. But then to -- the fact that we made no remarks and no characterization at that time and then to rescope these people six to eight weeks later and try and remember what that patient had, I mean, in a busy practice, that is not really practical.

DR. LEVY: I have a couple of other questions. There were four sites that had statistically-significant differences in adhesions only four sites of the available sites. I know that the surgical procedures were similar across all procedures in all sites. But do you have any data on those four specific sites of adhesions and what types of procedures were done in those cases where there were de novo adhesions that were not -- did you divided it out by those areas that were statistically significant? It seems odd that there would be only four sites with statistically-significant differences.

DR. MOSCICKI: I will certainly ask our statisticians to back me up on this. But, in response to that, again, the study was not powered or designed to try and specifically show statistical significance at individual sites. That would require a different approach probably. and so when you look at this in the aggregate, which was the way this was designed to be, you think that is what it was really designed to look at. I think that one might look at it conversely that, despite the fact that it was not designed to address that, that we were able to achieve statistical significance at four of the anatomical sites. To my knowledge, we did not conduct any analyses that

specifically addressed a type of surgery related in those cases where there was a success at those four sites. But I will also ask the statisticians. Okay. Thank you. Heather Kelly has indicated that we did not conduct that analysis. But certainly it is possible to do.

DR. LEVY: I have one other question. Could someone comment on the second look procedure in which there was an enterotomy. Obviously, that is a major complication and the kind of thing we are trying to avoid with adhesion prevention devices. I just wonder if we have any clinical information on that case? Was this a de novo adhesion? Was this something that had been present before?

DR. MORROW: Dr. Diamond, do you want to address that?

DR. DIAMOND: I know that with one of the patients the enterotomy that occurred was not at the time of entry into the abdominal cavity. It was a time of dissection, an operative component of a procedure -- component procedure as opposed to a diagnostic component of the procedure. Specifically, though whether it was a site of de novo adhesion formation or adhesion reformation, I do not have that data. I do not know if that is available.

DR. BEAVER: Eric Beaver, University of Chicago.

I have no financial interests. We were one of the principal investigators. This was not my site where this occurred. But, in reviewing the data, what apparently happened -- this was a laparotomy where the coating solution had been applied. At the time of the second look where an informal incision was made, there was an enterotomy from bowel attached in this area. So that was a source of the complication merely in insufflating and putting the truncar through they created an enterotomy.

DR. LEVY: Was that an adhesion though or was that just a bowel that was not adhesed?

DR. BEAVER: That was an area of adhesive attachment infrombulical (sic).

DR. LEVY: And we do not know, in that case, whether that adhesion or those adhesions might have been a priori adhesions or areas of surgical trauma or whether that is de novo adhesion?

DR. BEAVER: From the reports that we reviewed, that did not appear to be an area where there was initial -- in the initial surgery that there was bowel attached. So, in this case, it would be a de novo adhesion. Whether -- it would probably fall under the category of 1A, as this was not an area of directed trauma.

DR. LEVY: Thank you.

DR. DUNCAN: As a general surgeon, I am sort of curious about the clinical follow-up on some of these patients that you have had in this particular study, both the control group, as well as the treatment group. I wonder if you have any data or any follow-up on any clinical consequences such as we presented before of abdominal pain, knowing that that first presenter actually showed data that above 20 percent of the patients will have some problems within the first year? I am kind of wondering if you have any follow-up data on the treatment patients, whether they suffered any clinical adverse affects such as small bowel obstruction, abdominal pain or infertility versus the control group? Any early results?

DR. MOSCICKI: At the present, we do not have any data that we can attest to that would be anything other than anecdotal at the present time, but I think that it is an excellent idea to contact these patients and have a looksy at some point. Although, again, that would probably be anecdotal what we would be able to achieve naturally.

DR. MORROW: Susan.

DR. GALANDIUK: I have also one question as a surgeon who does a lot of surgery for cancer. Do you have

any animal experimental studies looking at the effect of using this in the presence of malignancy?

DR. BURNS: We have not completed any studies that have looked at that, although it is an area of investigation, but I cannot really comment on completion of any experiments at this time. This is a concern or issue for us as well. We have looked at the literature extensively and we do not see any indication in the literature that exogenously added HA is going to cause any increased problem in terms of seating or proliferation of tumor cells, but it is an area of interest to us and we intend to look at it in preclinical studies.

DR. MORROW: Dr. Levy.

DR. LEVY: I have got another question probably for Dr. Diamond. Was there any standardization? In fact, it is my impression reading through the materials that there was no standardization as to post-operative management of these patients. Do we know how many of these patients were treated with anti-inflammatory medications either pre-operatively, intra-operatively, or post-operatively?

DR. DIAMOND: There was not -- there was some standardization. With regard to these non-steroidal agents, there were approximately 10 patients in both the treatment

group and the control group who have received nonsteroidal anti-inflammatory agents. If you do statistical analysis to see if that effects efficacy, there is no significant difference between them. They are such small numbers it is very hard to know what to make of that.

DR. DESHMUKH: I have a question. What was the method used to instill the solution in the peritoneal cavity?

DR. MOSCICKI: Again, I will ask our investigators to address that. Perhaps Dr. Bradshaw --

DR. BRADSHAW: What was the question?

DR. MOSCICKI: Yes. The question was what was the method for installation during the clinical studies?

DR. BRADSHAW: I am Karen Bradshaw, at UT-Southwestern Medical Center in Dallas. I was one of the principal investigators, and I have no financial association with Genzyme. The procedure was very standardized. When we opened the abdomen, we instilled the solution, allowed it to remain in the pelvis for approximately one minute and then suctioned free the solution. If we needed to irrigate with Ringer's Lactate or another type of solution, we would reapply the Sepracoat at that time or the whatever we were using. And then we repeated the application every 30

minutes throughout the procedure, each time irrigating the pelvis, allowing it to remain in position for approximately a minute, and then suctioning it free.

DR. DESHMUKH: My question was why did they just install it with a cap and take it or spray-type device (sic)? Did all of the investigators use the same method?

DR. BRADSHAW: I believed that we all used the Ascepto Syringe and would get a quantity of Sepracoat or solution that was pre-approved 60 CCs, and would apply it to the entire operative site.

DR. DESHMUKH: Thank you.

DR. LEVY: Karen, before you leave, were you also applying it in the abdominal cavity? In other words, when you opened the peritoneum, were you assuring that you were coating the small intestine and the upper abdomen as well as the pelvis or were you just coating the pelvis?

DR. BRADSHAW: Well, initially, when the abdomen was open the available sites were irrigated. After the bowel was packed away, then we irrigated primarily in the site of operation which would indeed be the pelvis.

DR. DESHMUKH: Did you control the temperature?

DR. BRADSHAW: Yes. The solution was controlled for temperature.

DR. DESHMUKH: At what temperature?

DR. BRADSHAW: I do not recall.

PARTICIPANT: At room temperature.

DR. BRADSHAW: Room temperature.

DR. DESHMUKH: What was the temperature of the saline that was used? Was that the same?

DR. BRADSHAW: Room temperature as well.

DR. DESHMUKH: That seems odd because normally we do not use room temperature saline, we use warm saline for using it during irrigation during an operation.

DR. MOSCICKI: Again, the material is prepared so that the surgeon could not tell whether the material delivered was in fact Sepracoat or the PBS solution. So, essentially, they were both treated the same and delivered the same.

DR. LEVY: A follow-up on my question about installation. So intra-operatively, once the bowel was packed away, when you were reapplying the solution, whichever solution it was, were you soaking the laparotomy sponges that were coating or packing the bowel, as you were also coating the pelvis?

DR. BRADSHAW: No, we were not.

DR. DUNCAN: That brings up sort of an interesting

point. If the whole purpose of this is to actually decrease the de novo adhesions in other sites of the abdominal cavity, then why didn't you reinstall it in other sites of the abdominal cavity rather than the operative site?

DR. DIAMOND: The reason -- in order to re-instill it throughout the entire abdominal cavity, the packing would have had to have been removed, applied to coat the upper abdomen, and then the packing placed back. In addition to the disruptions to the procedure that this would cause if you did that on multiple locations, it would be the concern of additional damage to tissue by having done that multiple times throughout the procedure. A minimum of every half-hour the test solution was to be applied.

Also, a second corollary to that would be that the bowel, having once been coated, if it was packed away, it would not be likely to have the coating solution, whichever it was, irrigated off or removed by the manipulation of tissue during the operative procedure because it was out of the operative field.

DR. BURNS: I think it is important to point out that once the tissue is coated and it has a coating on the HA and it is then packed away, it is not as necessary to recoat that tissue, compared to the operative field where

there may be some drying out or irrigation.

DR. MORROW: Are there further questions for the sponsor?

DR. DESHMUKH: I had another question. He said that there is a possibility that some people might be allergic to this. Do you propose that they be tested for an allergic or hypersensitive reaction before using it?

DR. MOSCICKI: In the initial safety studies, we happened to find three individuals who had some urticaria, but we have not observed this at all in a very much larger number. As you can see, 334 patients were exposed. We have not seen any significant allergic symptoms.

I think that the FDA medical reviewer had also asked about whether we had seen any asthmatic reactions. Out of the large number of patients who had a history of asthma, there was only one who had had some post-op changes. So, again, we have not clinically seen any evidence of this. We also conducted skin testing studies early on in relationship to that, and were unable in skin testing studies to identify any pre-existing sensitivity in the normal population to any of these materials. I think that Dr. Burns had also mentioned that he has done animal studies regarding immunogenicity and was unable to identify any

problems there.

DR. GALANDIUK: Was that even looking at repeat administrations?

DR. BURNS: In the animal studies we were looking at repeat administration in our systemic allergenicity study.

I would like to also point out that hyaluronic acid, which is a polysaccharide, has been used extensively in ophthalmic preparations. To the best of my knowledge, there have been no reports of any immunological effects.

DR. MORROW: Any further questions?

DR. DOWNS: In the analysis of variance that was done to check for the effect of covariates on the treatment, were the covariates -- it is not clear that if I am reading the material whether the covariates were examined simultaneously in an all-inclusive model or one at a time in several successive models.

DR. MOSCICKI: Yes. I would like to ask our statistician to go ahead and address that for you since Heather Kelly had actually performed those.

DR. KELLY: The covariates were addressed one at a time in the model, with the exceptions of demographics where we looked at height, weight, and body mass index at the same

time.

DR. DESHMUKH: I have one more question. Many surgeons, including myself, use antibiotic irrigation at the end of the operation. Does this material cause any precipitation with different antibiotic solutions that people use like Vasopressin or Karomycin?

DR. MOSCICKI: I would like to ask Dr. Schwaitzberg to comment on that.

DR. SCHWAITZBERG: Steve Schwaitzberg. In addition to being concerned about the potential for infection with HA solutions, we were further concerned with the inability of antibiotics to perform their normal function in the presence of HA solutions. And we performed a lot of in vitro and in vivo testing of a variety of different antibiotics, not every antibiotic under the sun, but some of the more common antibiotics and found that they performed normally, and had a normal MIC to the bacteria that were tested which were Staph, E. coli, candida and necorotis.

DR. DESHMUKH: But there is no physical reaction like precipitation that you noticed?

DR. SCHWAITZBERG: No. None of the antibiotics precipitated,and they all had their normal antibiotic

activity.

DR. MORROW: Thank you. At this moment, we will recess for a 15-minute break. There will be an opportunity for further questions after the FDA. We will convene at 10:40 promptly.

[Brief recess.]

DR. MOSCICKI: In just one minute we will start with the FDA's presentations, hear the complete presentation and then have time for questions again afterward.

Agenda Item: FDA Presentation

DR. BERKOWITZ: Okay. Thanks you, Dr. Morrow. We would now like to begin the FDA presentation of P960003 or Sepracoat coating solution.

I am David Berkowitz. I was the lead reviewer and I would like to acknowledge the review team. The medical reviewers were Dr. Horowyj and Dr. Schultz. The statistical reviewer was Dr. Lin, and the preclinical studies were done by Dr. Zeropeli, Dave Kaplan, Paul Williams, and Anthony Watson.

The plan is that I will give a quick overview of the preclinical studies. Dr. Horowyj will then do the medical review, and she will be followed by Dr. Lin, who will do the statistical review.

So, again, Sepracoat coating solution is a four-tenths percent solution of hyaluronic acid actually buffered to neutrality. The viscosity is in the range of 300 to 500 CP. The molecular weight is about 1.3 million, but it is actually controlled once the viscosity and the concentration are specified. The molecular weight is, in essence, specified. This is a normal constituent of the extra-cellular space and is common in fact in most animals.

The effectiveness was discussed by Genzyme. The model is primarily the rat abrasion model. For example, in a three-laboratory round robin study, Sepracoat reduced the number, the percentage of animals with adhesions from zero to 17 percent, that is through the range over the three laboratories. I am sorry, the control was zero to 17 percent of animals with no adhesions. In the Sepracoat group, 33 to 72 percent of the animals had no adhesions.

I would like to point out just again that the action of Sepracoat is to prevent the -- to reduce the abrasion or to reduce the insult which causes -- which would later form adhesions rather than acting as a barrier toward adhesion production itself.

So I think they have done many experiments. The data are certainly strong enough to support -- the evidence

will certainly support testing in humans.

Now, the general toxicity testing was also reviewed by genzyme. Again, this was pretty much the same list. The first group is sort of the general biocompatibility group. In general, we would not expect, since this is a normal constituent of the extracellular space, we would not expect to find it to be noncompatible. Likewise is sort of the general cytotoxicity/toxicity group, the second group. These also were completely negative.

Acute toxicity was studied subcutaneous in mice and intra-peritoneally in mice and they also were negative, as were the intravenous toxicity that was studied in the rat. But when it came to studies of the baboon, the results were somewhat different. The baboon experiment was very different. The animals were very carefully monitored. They did clinical laboratory tests on some of the coagulation factors, CBCs, blood cells, et cetera. In addition, the animals had cardiovascular monitors in. So the monitoring was much more extensive and the baboons were infused in a rapid intravenous infusion with 10 percent of the blood volume of hyaluronic -- of Sepracoat.

Two results came out which seemed as though they might be significant. One was a 10 percent decrease in

cardiovascular output which lasted only one hour, and the second was actually a doubling in the bleeding time. In order for the bleeding time to get back to normal, it required three days. So that was quite a while. We thought that both of these may be important since the high-end of the dose range for Sepracoat is one liter and that is even more than 10 percent of the blood volume considering a 70 kilogram person. But, of course, it is applied intra-peritoneally rather than intravenously.

The bottom line is that we think that neither of these do turn out to be a problem. First of all, on the baboon, the effect was seen at 10 percent of the blood volume and not at five percent. So the highest dose is required in order to see the effect. Secondly, I should put out -- I should mention that with Sepracoat, although a liter is put in, the excess fluid is also removed and so it is not the full dose which -- the full high dose which is applied does not really remain in the abdomen.

From the clinical study itself, it turns out, if we look at handling characteristics as an example, the control group had fewer -- the control group, if anything, had fewer hemostatic problems. The treatment group had fewer hemostatic problems in the control group.

In the adverse events list, in fact, there were four hemorrhagic events in the treatment group and six in the control group. So there is no evidence that any of these factors carried over in the clinical study.

Finally, in this 12-week intra-peritoneal rat study, these animals were exposed to what would be the equivalent of more than four liters per 70 kilogram person and those animals always all appeared to be normal. So we believe that the effect probably will not carry over and the intra-peritoneal route is obviously very importantly different from the intravascular. And the pharmacokinetic studies which follow show that effect very nicely.

This experiment was done by using uniformly-labeled hyaluronin and putting these into rats intraperitoneally and then measuring radioactivity in various tissues. The peak here represents the peak blood level of the radioactive hyaluronin, and that occurred about 10 hours after the material was infused into the peritoneum. So that indicates that the absorption of the material from the peritoneum is quite slow. At this point, at this 10-hour point, 35 percent of the material had already been metabolized. Most of the metabolism is through the lung. It is exhaled as CO2.

I think that the next slide shows, if we look here, in fact, the cumulative excretion of radioactive material. You can see that at this point, at this 10 percent point, you have to look at the 10 percent point, but, nevertheless, 35 percent of the material had already been excreted at the time of the serum peak.

Also, I should point out that the height of the peak only represents about 15 percent of the administered dose. So the actual blood levels of the material never get very high.

Finally, there are some special considerations also brought up earlier. Pharmacokinetics we have already talked about. The infectious potential was examined in several ways. One was done in some in vitro effects by looking at the effects of antibiotics in vitro to see whether antibiotics were as effective. And, as we have already heard, they were as effective in inhibiting the growth of microorganisms -- they were equally effective with and without Sepracoat.

Secondly, there were also some -- there was no effective growth -- that is Sepracoat did not stimulate the growth of the microorganisms as well, also determined in vitro.

The second experiment was also done in vivo, that is the various microorganisms were implanted into the peritoneum of rats along with or without Sepracoat and, again, Sepracoat did not stimulate -- in fact, did not inhibit it. As it turns out, when microorganisms were put in, the titers actually fell about four logs, and that was true whether or not Sepracoat was present. So there did not seem to be any effects on the effect -- that is the device, Sepracoat, had no effect on the infectious potential of the microorganisms.

Finally, an important question is since many of the mechanisms that are responsible for healing are the same mechanisms which cause adhesions, it is important to know that Sepracoat did not inhibit healing. This was determined in an intestinal anastomotic experiment. What they did was sever the intestine, re-anastomose it in the presence and in the absence of Sepracoat, and then measure after that seven days later, I believe, measure the bursting pressure. And bursting pressures were the same for both the treatment group over the control group. So there was apparently no effect on anastomotic ilk.

So, we believe to summarize that there are no effects that were detected preclinically which directly

translate into -- we would guess would translate directly to human safety problems. That is the end.

Now, I think that Dr. Horowyj will continue with the clinical.

DR. HOROWYJ: Hi. My name is Roxy Horowyj. I am a chemical engineer as well as a general surgeon and critical care surgeon, working at the FDA now as the medical reviewer for the General and Plastic Surgery Advisory Groups. I will be presenting the clinical review of the Sepracoat PMA.

My agenda will be to go over the background, as well as the clinical trials and, as well as the panel questions.

The peritoneum, as almost everyone here knows, is the single layer of epithelium with an underlying support layer of highly vascularized loose connective tissue. It covers all intestinal organs as well as abdominal cavity walls. It usually heals when wounded over a period of days by lymph contraction.

[Pause.]

DR. HOROWYJ: Adhesion formation, as we know, is a protective response to localized peritoneal insult, an adaptive healing response to bring blood supply to the skin

areas of the peritoneum.

The etiology. It is well-known. Tissue trauma is addressed in this product development and occurs by ischemia, abrasion, or desiccation.

Intra-abdominal infection is another well-known etiology. This is dealt with here by including it as an exclusion criteria for study patients. So patients with intra-abdominal infections that were known were excluded from the study.

Foreign body effect, however, was not controlled for nor assessed, so the foreign body effect of glove storage fibers from gauze or patenting, their affect on adhesion as an etiology, as well as their interaction with the product are not known at this time.

Adhesions can be classified, as you have heard, by site, the direct surgical site, or a remote indirect site, as well as whether they are new or free forming, meaning previously lysed. In this case, we will be focusing on the de novo adhesions, the new adhesions at the indirect and remote sites.

Adhesion incidence also has been reported to be over 90 percent in patients undergoing laparotomy. Morbidities due to adhesions include chronic abdominal

pelvic pain, infertility. Up to 20 percent of patients who present with infertility, as well as with small bowel obstruction in up to 80 percent of patients who present with acute small bowel obstruction. Therefore, attempts at post-operative adhesion reduction, prevention is warranted assuming that adhesion reduction decreases the long-term sequelae, the morbidity of adhesions, and also assuming that adhesion reduction is an adequate surrogate of the long-term sequelae and morbidity of adhesions. These have not been proven.

Sodium hyaluronate, as we have heard, is a simple unbranched hemoglycan and it is found in variable amounts in all tissues and fluids of adult animals. It is metabolized widely by the organism and excreted through the lungs mostly as CO2. It is implicated in the molecular basis of focal adhesion turnover, as well as in tumor cell motility and invasion and fibroblast mobility.

Sepracoat coating solution, as has been described, is a .4 percent by weight concentration of hyaluronin in phosphate buffered saline, which is controlled for viscosity by its dilution and its production for molecular weight. It is intended to reduce post-operative formation of de novo adhesions by providing a temporary viscous barrier that

reduces micro/macro injuries to peritoneal tissues.

In continuing product development, the Genzyme Corporation undertook multiple clinical trials. These were of two forms, a feasible trials and the pivotal trials. The feasibility trials focused on determining the safety and the interoperative handing of the Sepracoat coating solution. There were two of them. The first one, however, occurred in three parts, so there were basically three. The pivotal study focused on safety and effectiveness of Sepracoat coating solution. This will be the majority. I will briefly go through both.

The feasibility trials looked again at safety and handling. Safety was assessed by looking at changes in vital signs or laboratories, adverse events and serious adverse events. Handling was assessed by a six-parameter questionnaire which was filled out by the attending surgeons at the end of the procedure.

The first study showed three patients who had hives. These hives resolved without incidence and were thereafter found to be not device related by studies that were performed by the sponsor. These were immunologic studies. There were no serious adverse events that were device-related and handling was not thought to be

interfering.

The second part of the first feasibility study similarly looked at safety and handling and there were no device-related events reported. The handling was thought to be acceptable.

The second major feasibility study, I guess, looked again at the same parameters. In this situation, there was one definitive case of adverse events, and in this case there was a laparoscopy procedure, I believe, where visualization was hindered and required the procedure to be converted to an open process, and this was thought to be due to the Sepracoat coating solution being in situ. There were also 10 possible adverse events which included things such as fever, nausea, dizziness. The handling was acceptable.

The pivotal trial, which is the trial whose objective was to evaluate the safety and effectiveness of Sepracoat coating solution when used during abdominopelvic surgery.

The safety, again, was evaluated by vital signs, laboratory changes, adverse events, and serious adverse events.

The effectiveness was evaluated by looking at the ability to reduce the incidence and severity, as well as the

extent of post-operative de novo adhesion formations by preventing remote or indirect tissue trauma, compared to control which was phosphate buffered saline administered under the same surgical conditions.

There were multiple end points. Incidence was considered to be the primary end point. Severity and extent were considered to be the secondary end points.

The incidence was defined as being the presence of adhesions at second-look laparoscopy, at sites which has been identified to be adhesion-free and did not sustain direct trauma at the first abdominopelvic laparotomy. As you heard, there were common procedures of laparotomy were leiomyomectomy and adhesiolysis.

The end points for the studies were defined to be proportion of patients with de novo adhesions. There was some good algebra presented earlier. This simplifies it also a little bit. The number of patients with de novo adhesions divided by the total number of patients in a given study arm.

The second end point that was introduced was the proportion of available adhesions at first look with de novo adhesions at the second look for a patient. It can be illustrated in this way.

The primary end point of incidence through this study was retained, however, later on the sponsor showed us to drop as claims the secondary end points of severity and extent. These were however evaluated and so I will present them.

As mentioned earlier, the adhesion scoring method looked at 23 anatomic locations. This method, however, also looked at the severity of adhesions on a four-point basis, and the extent of adhesions on a four-point basis. The pivotal clinical trial design was a three-week randomization using .2, .4 percent -- .2 percent hyaluronic, .4 percent hyaluronic, and control. The control was phosphate buffered saline.

The masking was attempted by having the solution presented to the attending surgeon as an unknown. However, being that there is significant difference in viscosity, it was questioned whether or not that was a true masking.

The second attempt at masking was by planning to use an independent video reviewer, in addition to the attending surgeon real-time evaluation. However, the data that is presented is mostly based on the attending surgeon's real-time evaluation for reasons as you have heard presented by Genzyme.

The design was that of a 17-investigator/23 investigational site design, with a total of 362 patients who participated.

The inclusion criteria for the study included females who were 18 years-old or older scheduled to undergo gynecological surgery per laparotomy that would require a second-look laparoscopy at one week to eight months after initial surgery. These patients also needed to and be willing and able to provide written and informed consent prior to study initiation.

Exclusion criteria excluded patients who were younger than 18 years-old, may be pregnant or have cancer, have any medical conditions which could alter their metabolism or excretion of the product, any medical conditions which could interfere with device safety or effectiveness evaluation, any one who has severe allergies, history or active pelvic inflammatory disease, or require insulin, such as Dextran, Heparin, corticosteroids or NSAIDS, or anyone who would be receiving any other kind of additional adhesion/anti-adhesion therapy, such as GORE-TEX or MC.

The sample size was initially proposed to be such. During the study, however, the sponsor decided to focus on

.4 percent high-viscosity solution as their focus product. So, in doing that, the sample size was then recalculated. Being that patients had already been enrolled into the study in all four groups, these patients were all retained for evaluation of safety. However, results for efficacy or effectiveness were only based on the patients who were in these two groups.

The numbers here, as you see, are different because there were patients who dropped out for reasons that they could not or did not -- the attending physicians felt they would not be appropriate to have secondary procedures.

The sponsors presented baseline demographics that were similar amongst the two groups. There were no statistically-significant differences between the groups.

The patients when looked at from the viewpoint of pre-treatment adhesions presented in this sort of distribution. The distribution looks similar, however, statistically it was found that the control patients had more pre-existing adhesions than the Sepracoat-treated group. We will be asking the panel to comment on their thoughts as to the clinical significance of this if any, no matter what the statistical significance may be.

The Sepracoat treatment procedure has been

described as being conducted in three ways, or three stages: The initial application, the repeat applications, and final application. The total treatment was to be no more than one-liter of solution maximum. Each application was performed over at least a minute over which all excess fluid was to be suctioned out.

The times to second-look laparoscopy were similar for the two groups.

The volume of solution applied and removed were similar, however, it is important to remember that the amount that was received, while that is accurate as to the amount of Sepracoat that was given to a patient, the amount removed included any other irrigants or body fluid that may have been to be suctioned out, so it was not determined as to how much Sepracoat was suctioned out. The numbers, however, are similar and in combination are not statistically significantly any different.

Handling characteristics were evaluated, as I said, by a fixed parameter questionnaire. This addressed: Tissue handling, instrument handling, suture placement, suture tying, achievement of hemostasis and view of the surgical field. As you can see, most of the time, there were no effects for handling characteristics. This is the

purple line here. This is enhanced effect, this is interference. This one down here that is very dark is a major interference which was only one time. And the green one, that window is missing. But the overall effect is there is no statistically-significant difference between groups for handling characteristics as evaluated subjectively by the questionnaire.

The safety was evaluated, as I said, with vital signs. In going over the outcomes there were no trends that were observed in vital signs in the groups.

The laboratory values, again, were considered by be consistent with expectations during the post-operative state. There is no relation to study that was identified.

The safety of adverse events were evaluated in multiple ways. This graph shows the various differences which were the 23, I believe, possible adverse events which were evaluated. The trends are similar between the groups. The most significant ones are for pain, which is unspecified, which is the first column, abdominal pain, the second, nausea, and fever. These were the most common and they were most common in all of the groups.

The adverse events, however, were statistically different between the hyaluronic groups, and this refers to

all of the patients that were treated with hyaluronic, not just the focused solution which was .4 percent high viscosity and the control. These were statistically significant for pain, both abdominal and unspecified, as well as nausea, dizziness and pharyngitis.

The investigating physicians at the time felt that there was no device relationship with these adverse events and they did resolve without sequelae. We will, however, be asking the panel to comment on the clinical significance of this.

Serious adverse events. There were 12 serious adverse events that were reported in patients who received sodium hyaluronic solution, and there were four serious adverse events reported in the control group. Most of these were not thought to be related to the device, however, there was a remote possibility that the patient who suffered pneumonia -- this was, I believe, a 20 to 40 year-old patient who had a history of asthma and smoking, who subsequently developed pneumonia, which quickly progressed to ARDS, requiring eight days of ventilation and, therefore, extended the patient's hospital course. She did recover and was discharged in good health possibly -- or discharged I should say.

The second serious adverse event that was thought to be possibly related was a wound hematoma, a superfascial wound hematoma that occurred in a patient on post-operative day nine.

There was one incident here, as we have been talking about bleeding. Bleeding has been mentioned in two patients, severe anemia and bleeding. One was in the control group. This was severe anemia, but this was associated with an estimated blood loss of 11 liters in the O.R., and it is reasonable to see severe anemia in such a patient.

However, there is a second patient here in the Sepracoat-treated group who developed a lot of subcutaneous hematomas. She is listed as having severe post-operative anemia. Here estimated blood loss was only .7 liters, and her hemoglobin was reported to have dropped from 14.2 to 6.6.

We will be asking the panel to comment on the clinical significance of these serious adverse events.

The effectiveness outcomes I will address at this point looking at the distribution of patients with de novo adhesions at available site after treatment. This is evaluation at laparoscopy, which shows the following

distribution.

As you have been shown, the Sepracoat group had about 88.8 percent patients who presented with de novo adhesions of available sites. Whereas, the control group had 95.4 percent patients with de novo adhesions at available sites.

As a summary, this may be sort of a busy slide, but it does summarize everything. I will try to go through it so that it is well understood.

The first bar graph there shows the incidence, which was the incidence end points, and mean proportion of adhered locations or locations with de novo adhesions. As you have both heard, the control group, which is the light blue, and the Sepracoat group is here -- the control group had .95, an incidence of .295. This translates to 4.75 adhesions or 4.75 locations with adhesions out of 6.1. So the 6.1 is the -- and the 6.9 are the average number of available sites.

PARTICIPANT: 16.1.

DR. WITTEN: 16.1.

DR. HOROWYJ: I am sorry?

DR. WITTEN: 16.1.

DR. HOROWYJ: I am sorry. 16.9 and 6.1.

DR. WITTEN: 16.1.

DR. HOROWYJ: 16.1 and 16.9.

So, in the end, the difference was 3.99 or four out of 16.9 and 4.75 out of 16.1. So there was a reduction of about .65 at each site on the average. If you take and divide .7 by 16.5, which is the average between 16.9 and 16.1, it is about 4.5 percent difference.

Moving on to the second incidence end point, patients with adhesions, as I said before, there is 88.8 percent and 95.4. I also plotted the results for mean extent of adhesion and the mean severity of adhesions.

So despite what statistics may say, we will also ask the panel to just consider what the clinical significance of these results would be.

I will present the questions. The first question was on baseline patient characteristics. The PBS group was found to have statistically more 4.5 versus 3.2 pre-treatment adhesions. The question is is this difference in patient characteristics clinically significant to the assessment of four percent high viscosity or Sepracoat coating solution effectiveness?

The second question is based on FDA CFR regulations. I will read this just to make sure that

everyone has the same baseline understanding. The regulation for safety says: For determination of safety and effectiveness, there is a reasonable assurance that a device is safe when it can be determined that, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. Valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

With that in mind, I will ask the questions about safety of adverse events. This was the results of adverse events. The question is is this statistical difference clinically significant to the assessment of safety in the four percent group? Meaning that the four or five parameters that we showed that had statistical difference -- is that statistical difference clinically significant?

The safety and serious adverse events. Again, as mentioned, there were no definitive relations for investigating physicians, accept for remotely pneumonia, ARDS, and possibly wound hematoma. Are these events and

those mentioned above clinically significant to the assessment of the safety of four percent high viscosity Sepracoat?

The effectiveness, again, is described in the CFR as for determination of safety and effectiveness that there needs to be a reasonable assurance that a device is -- or there is a reasonable assurance that a device is effective when it can be determined that, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use will provide clinically-significant results.

The questions on effectiveness are, in viewing the mean proportion of patients with de novo adhesions, being 88 percent for the Sepracoat group and 85.4 percent and 95.4 percent for the control group, is this reduction in the number of patients with de novo adhesions clinically significant to the assessment of Sepracoat effectiveness?

So, when looking at the second end point, which was the mean proportion of available sites with de novo adhesions for patients, and the results being as follows. Is this reduction in de novo adhesions clinically significant to the assessment of four percent high viscosity

hyaluronate or Sepracoat coating solution?

The last question, and one that has been sort of touched upon today is the clinical significance. Protocol HC911203 utilized the incidence of de novo adhesions as a surrogate end point for long-term sequelae or morbidity of adhesions such as chronic abdominal pain, infertility and small bowel obstruction. The surrogate end point has not been validated. We would like to ask the panel what steps should be taken to validate this end point so as to demonstrate the clinical benefit that adhesion reduction as for Sepracoat coating solution is effective in reducing the long-term sequelae and morbidity of adhesions. Thank you.

DR. BERKOWITZ: The next speaker will be our statistical reviewer, Dr. Lin.

DR. LIN: Okay. Dr. Morrow and members of the panel, I will present to you some of the issues from the statistical point of view. I will focus on the Sepracoat effectiveness. So my comments will focus on the effect of the pivotal effectiveness study of HC911203.

I have organized my presentation as follows: Sponsor's results are summarized, then the written analysis and the why, how, and findings from the analysis will be presented, followed by comments on the trial end points

issue, the sample size implications on the statistical tests will be discussed, and then I will give a summary.

For clarification of some of the terms I use in my presentation, for anatomical site I will use the word location. Otherwise, I use the word site, investigative site, meaning investigators. And the database that I have received I had only 16 investigator sites that contributed to the comparison between the treatment with Sepracoat and PBS.

I will use interchangeably among the three designations for Sepracoat in this presentation.

I also want to note that in all of the P values that are put in this presentation will be one-sided because I do not think that we should make a big deal out of -- based on one-sided/two-sided issue.

This slide summarizes the sponsor's results. As you can see, the control group/treatment group, there were 108 and 107 patients respectively in the intend-to-treat population.

Post-operatively the incidence was defined as a percent of patients who have one or more de novo adhesions was 95.4 percent in the control and the 88.8 in the treated group. The numbers came out to be 103 out of 108 in 95 and

107.

The incidence was defined as the average proportion of the available abdominal locations with de novo adhesions as, as you have seen, 29.5 percent and 23.6 percent in the treated group. The P values presented in the PMA were .0621 for the incidence as a percent of patients and .0125 for the incidence and the proportion.

I made a note here saying that this perhaps is the correct T value to be attached to these numbers over here as I will show on the next slide.

This is a busy slide, however, please pay attention only to the square here and here. These numbers were derived by doing two sample T tests. The numbers in the left-hand square you have seen already. They provide the average proportion, as an end point for de novo adhesions. They were 29.5 percent and 23.6 percent for the two training groups. The correct T value associated with this difference here, according to the T test is this number. There is no reason why this number should not be attached with this difference here according to the T test. The end point of de novo adhesions was also analyzed after Arcsine transformation. The T test for that end point came out to be .125. It was this T value that was attached to

this difference here.

The previous slide not only verifies the sponsor's results according to the T test, it also shows the need or verifies for myself that when I look at a real analysis, I will be looking at the same data set as the sponsor had in their T test analysis.

The reason that we want to look at perhaps more than T tests is that this pivotal trial design was multi-site and it was randomized, and the T test will not incorporate any of those futures in the analysis. To incorporate the multisite nature of the clinical trial, it can be done easily by using the basic statistical methodology analysis of variance.

Now, when I look at the data and I tried different models, but in all of them two effects came out to stand out very significantly, and they were the side effect and the treatment by site interaction on the original proportion of de novo adhesions as well as Arcsine transformed analysis.

Again, here you see the effect and here it gives the significance of that effect in the analysis. Some are here for the Arcsine transformed and their P values. This says that we have very significant side effects that is that the treatment response varies significantly across sites.

Now, that in itself is not a problem.

Site interaction here. This is highly significant according to this end point and very significant over here as well.

There are two kinds of treatment by significant interactions, namely, a quantitative one and a qualitative one. A quantitative one is one where the treatment effect size is not homogeneous but it changes across site significantly. That is not a major concern, however, in this pivotal clinical trial, the treatment by site interaction was a qualitative one in nature. That poses a serious problem. As we have seen perhaps earlier, this was attributed to the response from site number three.

I have a couple of comments here. Even though the investigator from site number three might no have been well or fully-trained in the beginning part of the trial, however, there was no evidence that he would have biased the adhesion scoring one way or the other against either one of the treatments PBS or Sepracoat.

The other thing I want to note is that I will think that the investigator from site number three would have been -- site number three is one of the largest sites. Therefore, I would think that the investigator from one of

the largest sites should have been fully-trained or well-trained at some point in time during the trial.

When the sponsors says about that -- and the answer I received was that, yes, perhaps sometime in about the middle of the trial the investigator should have been well trained or properly trained.

Now, site number three in total had 34 patients. So, in the middle of that, when I look at the database, it corresponds pretty much to the time when the decision was made to develop only the high viscosity product. So, I deleted those patients who were enrolled before that time and noted, first of all, that most of these patients were control patients and that there was no significant difference between those patients enrolled before the decision and those made after the decision the control group. Of course, the sample size was not large enough to really detect a significant difference.

However, looking at those patients only after the decision, the trend for the significant treatment by center interactions persisted. In fact, I included only those patients enrolled after the decision. You see that the treatment by site interaction remained very significant.

The treatment by site interaction remained very

significant according to their original proportion or entrance form. Given that the trial was never designed to show an interaction effect and that is not a -- that -- that says that the interaction persisted.

I also wanted to point out that, other than site number three, there were at least two other sites that came out to be negative in treatment effect, meaning that there response was better with the control group than the treated group. I will have a slide later on to illustrate that.

So, it appears to me that the explanation given is not fully satisfactory.

Okay. The significant treatment by site interaction for the end point proportion of de novo adhesions makes its data probability highly in question. I also note that significant interaction were also observed for the mean extent, median extent, mean severity and median severity.

Okay. Statistically, the significant treatment by site interaction is that one cannot attach a statistical significance to the treatment effect comparison without bias because now we have a multiplicative model instead of an additive one. That, in effect, invalidates the P values for treatment comparisons.

Subsequent attempts at post-op subsequent analysis is usually inappropriate. But what one can do is to list the treatment differences by site and make an overall clinical judgment as to the significance.

This next slide I will explain. This slide attempt to show just what I said. You have on this axis here the investigator sites, and there were 17 of them in all, but, like I said, there were only 16 who contributed data between the two treatment groups. The end points we are looking at in this case is the do novo, the proportion of de novo adhesions. On the Y axis over here is the difference in the proportions for those two treatment groups. You take the difference. That is a measure of the treatment effect for each of the sites.

Now, for each site here, you have a dot. The center of the dots, let's take this one here, measures the treatment effect, the treatment difference. That is an estimate. And the size of the dot approximates the sample size for the site.

So, for instance, we have about one, two, three four, fairly large sites. Actually, the largest of these had 24 subjects and the smallest had about eight. I wanted to point out, as I said earlier, there are negative sites

which contribute to the significant interaction effect.

The other incidence end point which was defined as a percent of patients with one or more de novo adhesions was also analyzed by use in the logistic regression. Even at no treatment by site interaction was detected, but there was a significant site effect. That is not a problem. We simply adjust for that. Adjusting for it revealed no significant treatment difference between PBS and the treatment.

Here I summarize the reanalysis results. As we have just seen, the incidence defined as percent of patients with de novo formations was not significant. That basically confirms the sponsors analysis. The incidence defines a proportion as well as these other end points, as I pointed out, had statistical problems in trying to attach a statistical significance to them.

I want to note that, as I said earlier, these P values were derived without adjusting for any of the factors from the multi-site trial.

I want to go to a different issue at this point. It is noticed that after listing all of these other end points, although the focus seems to be directed at the incidence here, however, in order to assess the significance, one has to go back again and look at the trial

design.

In the protocol is says that the application of the product to expose serosal tissue will form a temporary tissue protective barrier against surgical trauma which is intended to reduce the incidence and/or severity and/or extent of post-surgical de novo adhesions.

These are all the reports of the protocol. Again, under the statistical analysis section, it says that the primary analysis would be a comparison of the incidence, severity and extent scores of de novo adhesions in each of the groups compared to the control group. Also, this was mentioned in the consent form. Therefore, it seems that the trial was really designed as one with multiple end points. Therefore, to single out any one end point or, for that matter, the statistical assessment of significance for any end point must adjust for the multiplicity of end points in the design.

Just some comments on the sample size. The basis for the sample size was that an estimated incidence of de novo adhesions at second look, approximately 30 percent in the control, and the ability of the Sepracoat .4 concentration to reduce the de novo adhesions to approximately 10 percent. So that is an absolute difference

of 20 percent. That was in the protocol determined to be clinically significant.

Now, based on that difference and with a power of 90 percent, .05 level of significance and an estimated sample size of 76 per group was obtained. However, in the trial, actually, close to 110 patients were enrolled. And so the much bigger sample size enabled the testing for a much -- testing for significance for a smaller treatment difference.

This next slide will summarize the numerical results according to the real-time surgeon's evaluation of the de novo adhesions proportion. It is the proportion of de novo adhesions according to the real-time surgeons.

Most of the numbers we have seen before. They are 108 patients in the control, 107 in the treated group. The baseline number of available locations had a mean of 16.06 and 16.91. These two numbers are not statistically significantly different.

The proportion of available locations with de novo adhesions proportion had an observed means of .29.5 percent and 23.6 percent for the difference of 5.9 percent.

Looking at the number of available locations instead of proportion of abdominal sites -- let's look at

the number of available locations with de novo adhesions. This had an observed means of 4.53 and 3.83 according to the intent-to-treat population. That is a difference of .7 adhesions. That is less than one adhesion. It seems to me that that is the number before the panel for comment.

This slide shows the percent relative reduction in proportion of available locations with de novo adhesions.

So, we have seen the difference between two treatment groups, the 5.9 percent. That is a simple difference. And we take that difference and divide it by the proportion from the control group, 29.5, and you get a relative reduction of 20 percent. So the relative 20 percent reduction corresponds to an absolute reduction of 5.9 percent.

I will just summarize the things that I have talked about so far. The significant interaction effect poses significant problem in statistical analysis which says that extreme care must be exercised in trying to attach a statistical significance to the treatment comparisons.

The logistic regression on the percent of patients with de novo adhesions confirmed the results in the PMA, which is that the difference between treatment groups was not significant. If one end point is singled out for

statistical significance, the multiplicity must be adjusted.

We talked about the sample size in relation to treatment effect size. In this case, because of the problems for statistics to assign a significance level to the treatment comparisons, the clinical assessment of the treatment difference becomes very important.

The data that I have reviewed so far was based on the real-time surgeon's evaluation of de novo adhesions. Now, the protocol has stipulated that the effectiveness would be also evaluated according to videotape recording. In the scientific section of the protocol it says that the multi-center study will be conducted in a double-blind randomized manner. Data will be collected and combined where patients will be treated identically according to the same clinical protocol, review of video recordings and analysis of results will be conducted under blinded conditions.

This next slide is a table that I put together. The data was provided by the sponsor. So this gives a comparison of the de novo adhesions proportions according to the independent video recorder of reviewer's scoring.

Now, in this analysis, there were 104 patients respectively in the two treatment groups. The baseline

number of available locations had a mean of 14.8 and 15.4. Now, the difference -- these numbers are different from the previous numbers, according to the real time surgeons because the numbers are different here. Perhaps the quality of scoring might not be the same. So they are a little different. However, this difference is not significant.

Looking at the proportion of available location with de novo adhesions, they had means of 27.4 percent and 22.6 percent control group and treated group. That is a difference of 4.8 percent. The P value given was .1. So that was not significant.

That concludes my presentation. Thank you.

DR. MORROW: Thank you. Do any of the panel members have questions for any of the FDA presenters? Dr. Azziz?

Agenda Item: Questions and Answers

DR. AZZIZ: Quick question. You have 16 sites in your database, yet there were apparently 18 investigators. Could you --

DR. LIN: 17.

DR. AZZIZ: 17 investigators. We are missing a site there? What happened?

DR. LIN: I remembered it was 16. I think it was

site A that did not contribute to the comparison data between the high viscosity and the control. Perhaps that site had other data. Earlier in the development process there was the low-concentration product that was evaluated.

DR. AZZIZ: But did the sponsor use that site's data for effective analysis or not?

DR. LIN: Not between .4 high viscosity deviance. There was no data.

DR. AZZIZ: So, for that -- so, for that we only have 16 sites?

DR. LIN: For the effectiveness --

DR. AZZIZ: It is .4 versus PBS?

DR. LIN: Right. There are only 16 sites.

DR. MOSCICKI: Yes, there were in fact 17 sites. The 17th site that Dr. Lin may be referring to did contribute PBS control patients.

DR. MORROW: Thank you.

DR. LIN: Well, what I am referring to is that I based my reanalysis on the data provided by the sponsor on diskette. In that I did not see 17 sites contributing data to the comparison, but I do not know how the issue that is --

DR. MOSCICKI: I have just been corrected. That

is right. I guess that site was contributing other patients that were not included in that.

DR. MORROW: Thank you. I think that the panel has the sense of that issue. Dr. Downs.

DR. DOWNS: You said that you compared the 80 controls in state one to the 40 controls in state two?

DR. LIN: No, I did not do that.

DR. DOWNS: Oh, okay. I misunderstood you.

DR. LIN: I did that for the one single site, site three.

DR. DOWNS: I see.

DR. LIN: My emphasis was trying to get a hold of the nature of the interaction.

DR. MORROW: Dr. Galandiuk.

DR. GALANDIUK: I have a question for Dr. Harowyj. On the side-effects that you showed, I mean, my concern, if this is excreted as carbon dioxide would be that, if you had a patient with COPD, they might develop hypocarbia post-operatively. Were any of the age groups of these patients of an age or did they have COPD and was that looked at?

DR. HOROWYJ: I am sorry, the age group?

DR. GALANDIUK: Did any of the patients have COPD or was the possibility of hypocarbia at all looked at in

these patients since this stuff is excreted as CO2?

DR. HOROWYJ: There were multiple patients, as far as I know, with asthma, but I do not know of the specific COPD diagnosis, and I have not seen a hypocarbia analysis. I think that would be interesting.

DR. DESHMUKH: I have a question for Dr. Lin. The picture that is shown with those round dots of the various centers. There are obviously some circles that are clear below and some were above. How many patients were in the circles below and how many were in the circles above?

DR. LIN: The big dot had 24 patients. The two smaller dots, I believe they had eight and nine respectively.

DR. DESHMUKH: Can you give any numbers? How many were above and how many were below?

DR. LIN: You are talking about how many dots above and how many dots below or number of patients?

DR. DESHMUKH: Number of subjects.

DR. LIN: Number of patients. The big dot below had 24 patients. The other two had eight and nine respectively.

DR. DESHMUKH: And how many were above the line?

DR. LIN: You figure that there were 212 patients

altogether, and so you take the difference.

DR. MORROW: Are there any further questions?

[No response.]

DR. MORROW: All right. At this point, we will adjourn for a one-hour lunch break.

[Whereupon, the meeting was recessed for lunch at 12:00 p.m., to reconvene at 1:00 p.m.]

A F T E R N O O N S E S S I O N (1:05 p.m.)

DR. MORROW: We're going to resume the afternoon session now. We will begin with comments from the panel primary reviewers. The first comments will come from Dr. Duncan.

DR. DUNCAN: I'm Dr. Titus Duncan, a general surgeon and Chief of Endosurgery at Georgia Baptist Medical Center, and Clinical Professor of Surgery at the Medical College of Georgia, as I mentioned before.

What I would like to talk about today is from a general surgical standpoint. The clinical view from a clinical surgical standpoint of the data that we have seen earlier today somewhat, but my basic concern is what the overall general surgical output or generalizable output is going to come about as far as these results concern. So I would like to just go over it with you briefly from my particular viewpoint as a clinician.

Now I put these slides in there at first, and this was actually my talk on laparoscopic hernia repair. Then I left them there, and I said this may have some significance as to the analogy of what we are talking about today.

This list actually comes from a list of around about 40 procedures that have been done for hernia disease

over the past century. You see here in 1877 to 1978 this list here includes about 10 types of hernia repairs.

Now most of the surgeons and most of the non-surgeons and primary care physicians know that a hernia is a very simple problem. It is a hole in the abdominal wall. As you see over the past century, we have had 40 different ways that we can actually repair a simple hole in the abdominal wall.

On top of that, the controversy regarding laparoscopic hernia repair or angel hernia repair or open hernia repair is so hot that sometimes at these meetings you get into sort of physical exercises with the surgeons there.

So I thought this was sort of an apropos slide, because what one of my old professors once told me is that anytime you have this number of procedures to correct or to fix a very simple problem, the chances are that not one of these procedures is the answer. Not one of these procedures is very good at actually doing the job.

This has pretty much been depicted over this past century by our recurrence rates with hernia repair, being anywhere from 15 percent up to 30 percent. It wasn't until we began to understand the pathophysiology of the defect and the pathophysiology of the biomechanics of the repair itself

recently, that we began to understand how we can reduce this rate of recurrence with the hernia repair.

We think that we have done that over the past couple of years with some of the tension free repairs that we do with Liechtenstein(?) type of repair and the laparoscopic repairs. I will come back to this slide in a little bit, but it pretty much has a good analogy to what we are actually talking about today as far as the number of products that we tried over the past several decades with anti-adhesive methods.

This is what we are talking about, adhesive disease. As people have mentioned before, adhesions are significant whether they are single adhesions or whether they are multiple adhesions. This is a patient went in on. The patient had a small bowel obstruction, and the small bowel obstruction apparently came from the fact that this small bowel was wrapped around as a single adhesive band. That small bowel was unbobulized(?) and the band was released, and that patient did okay for now.

Now I want to go to the etiology of adhesive disease. Now the majority of the problems that we are going to see as surgeons and gynecologists with adhesive disease is primarily going to be down in this category here,

surgical. There is no question that a good percentage of the causes of adhesive disease fall into this category as non-surgical. Any sort of inflammatory process that occurs in the abdominal cavity can incite that cascade of adhesion formation, including PID, patients with appendicitis, Crohn's disease diverticulitis and cholecystitis.

One of the most common type of adhesions that we are seeing is in patients who have diverticulitis, and you look inside there and those patients have adhesions of the sigmoid colon up to the abdominal wall. We are not going to discuss these so much. We are going to pretty much focus our concentration on the surgical or post-operative adhesion process.

As someone mentioned earlier today in their talk, there is no question that patients and surgeons and primary care physicians and the community in general, especially the economic community, releases the problems and the complications that adhesive disease will cause -- abdominal pain, both acute and chronic abdominal pain.

I see it; because I'm a laparoscopic surgeon, I see a number of patients who have chronic abdominal pain with previous abdominal surgery, and with all our work we can't find the cause of the abdominal pain, and we want to

go in there laparoscopically.

It can cause problems with infertility either from direct obstruction of the ovan duct, or adhesions latched on to the ovan duct and causing dismotility of the ovan duct itself; small bowel obstruction, both acute and chronic; as we recently found out that you can also get some large bowel obstruction from adhesive disease as well; and pelvic pain are common complications of adhesive disease. Like I said before, it poses a significant morbidity for the patients, and it poses a significant economic impact to our health care delivery system.

Here are some of the slides that we see with adhesive disease. This is what they look like when we go inside. This patient had come in with chronic abdominal pain, and when we went in there laparoscopically, we see they had adhesions to the uterus, adhesions to all sides of the pelvic wall. We took these adhesions down and that particular patient did okay.

This patient had a small bowel obstruction from adhesive disease. We found this portion of collapsed bowel, followed it back to the area of adhesive obstruction, latched the adhesive obstruction, and collapsed the dilated bowel down in this area here. The last of the obstructions

and the adhesions were taken down subsequently.

This is a patient who had chronic infertility problems, and chronic pelvic pain all at the same time. You can see the uterus is up here. They are actually on both sides, and they had the right side completely emerged with adhesive disease. The cul-de-sac is completely emerged with adhesion disease. So there is no question that adhesions like this causes significant problems in both patients and the surgeons as well.

Now this slide was shown here earlier today, and I won't dwell on it too much, but we have pretty much gotten behind what causes adhesions, and pretty much tried to approach in the 1990s, the treatment for adhesive disease or the prevention of adhesive disease based on this particular cascade.

This cascade follows that you have intact cirrhosal(?), with intact mesothelial cells, and at some point in time you get the cirrhosal injury and declamation of mesothelial cells. That excites an inflammatory response, and that inflammatory response cause release of cellular elements, those elements being cytokines, erythrocytes, lipocytes and platelets.

In the appropriate environment where you have

adequate oxygenation in this area, you have positive plasminogen activated, which then latches the frigrand(?), and then you go back and get normal mesothelialization and don't have any problem.

In the more common environment, in the hypoxic, we decrease the concentration of plasminogen activator. Plasminogen then converts to plasma, and so you don't get the latching of adhesions, and instead you get subsequent adhesion formation with deposition of fiber.

So I characterize adhesion for invention in two basic categories: the non-barrier methods, and the barrier methods. Now the non-barrier methods we are all familiar with, and I just basically want to go over these very briefly, to show you again that over the years we have tried all of these things, and again, when you have this number of things that you are actually trying, chances are that not any one particular item is simply that good.

We tried perinatal lavage when I was a resident. When I was a resident, my attending always told me to copiously irrigate out the abdominal cavity and continues to do that with things like renous lactate solution. What he said renous lactate does is that it decreases the swelling of the mucosa of the cirrhosal, the mesothelial cells. It

also washes away the fibrinous extrudate, and it also prevents desiccation. That's a perinatal lavage. How well that works, we don't know just yet, but a lot of surgeons do them. At my time in residency training, they felt that it was a good alternative.

Agents affecting coagulation, the most common being the use of heparin. Heparin has, as far as I'm concerned, two basic effects. Number one, it inhibits clotting. So when you have a bunch of clotting, you have obviously a nice scaffold for fiber deposition to occur.

It also has a tendency to activate tissue-type plasminogen activator. With that plasminogen activator being activated, you increase the plasminogen conversion to plasma and it increases fibrinolysis.

Steroids, on this round this cycle here. Most of these products that we're talking about access some point along this cycle. So steroids, and even non-steroid inflammatory agents try or make an attempt to decrease the inflammatory response, and therefore decreases the adhesion process.

Calcium channel blockers, such as Verapamil increase the tissue oxygenation of say the level by releasing a potent vaginal dilator, and therefore you get

the decreased amount of epoxy, which inactivates the plasminogen activator, and therefore decreases adhesion formation.

Prostaglandin is not the sort of anti-inflammatory drugs we are going to talk about.

Tolmetin is an interesting drug. It is an arachidonic inhibitor. It supposedly increases the number of phagocytes in the area that actually chew up the fibroblasts and any other material that is responsible for making adhesions.

And then tigitype(?) plasminogen activated, like I said before, helps convert plasminogen to plasma, and that increases the latches of the adhesions.

There is a second weapon of adhesion prevention, which is actually the barrier options. This what our primary concern is going to be today. Dextran has been used for a long time, and that is basically sort of a glucose polymer that has a sort of a silicon effect if you will. It makes the bowel nice and slippery, so it prevents the apposition of the mesothelial cells from the perineum or the mesothelial cells from the bowel to the mesothelial cells of the bowel.

Polyxamer 407 is a co-polymer, combined with

polyaxy propylene and polyaxy ethylene. It has a sort of funny effect, that at cold temperature it is a fluid, but at body temperatures it actually turns into a gel. So when you inject it into the abdominal cavity, it forms a gel, and again, that gel acts as any other gel, as a barrier between the mesothelial cells.

Bioresorbable hydrogel does pretty the same thing. Carboxymethyl cellulose is the same thing. We haven't had a whole lot of good success or reports of good success with these particular products.

Goretex membrane is sort of an interesting product. It is something that is a non-reactive and non-degradable expanded polytetrafluorethylene product. It has a great tendency to decrease adhesion formation or adhesion adherence to the material itself. The problem is that it is a permanent thing. It doesn't resolve, and it has to be left in there permanently, and it has to be fixed in place.

Oxidized regenerated cellulose, endiseed(?) or certacell(?) is pretty much a woven-like structure that you put inside the abdominal cavity, and has the advantage that it doesn't have to be sutured in place, and it resorbable. Again, it degenerates into a gel-like mass, and again, prevents the apposition of the mesothelial cells.

What we are here to talk about today is hyaluronic acid. Hyaluronic acid, as we talked about it this morning, you pretty much know its affect. It is a hydrophilic, high molecular weight polymer, and has been used for a number of ophthalmologic procedures already in the United States, and has also been studied in animal models.

When applied after the injury has occurred, it has failed to reduce adhesions, but as we mention here, when applied before desiccation or injury to the mesothelial cells occurs, it actually has a tendency to decrease the overall adhesion formation.

The question that I have, and the question that is hopefully going to be involved in the panel discussions later on is how well does it do that? If it does it significantly, are we going to eventually see some significant clinical results?

The bottom line, as far as I'm concerned, is the clinical results. Are my patients going to go through life after I put this particular product in all of their abdominal cavities, with or without a chance of having post-operative problems such as abdominal pain or infertility, and so on and so forth.

They have come up with a nice little method to

grade adhesions. There are type 1 and type 2 adhesions. The ones that we are going to be talking about today here are the normal type of adhesions that are called 1A adhesions. They are the development of adhesions at sites that did not have any adhesions initially.

In other words, if I go inside a patient and go in there to do a gall bladder operation, I look down in the abdominal cavity in the ringal part, and it has an adhesion there, that's called a type 1 adhesion.

Type 2 adhesions is after we have been in there and we have operated on the patients already with our heser(?) lasers and we re-look at them again, those are type 2 adhesions if they have adhesions that are reformed in that area.

Type 1A, as I mentioned before, no operative procedure at the site of adhesion formation, which is what I'm going to talk about today with this particular product; and 1B, operative procedure performed at the site of the adhesion formation.

This is actually a patient that I did an appendectomy on. Sometimes surgeons get a little jealous, and they put their hand down a cavity to feel around, especially if the appendix is normal. Then they want to

kind of feel around and make sure the stomach is okay, and the feel in the upper abdominal cavity.

This is what I feel may be type 1 adhesions. Now I'm not exactly sure how much trauma I induce by putting my hand up in the area, but I operated in the right lower quadrant, and the adhesions, when I looked back in there a second time, or in the right upper quadrant above the liver. So these may be classified as type 1 adhesions, adhesions that are in a remote site from the area that you operated on before.

These may be classified as 1B adhesions. This is the liver here. This is a patient I did a gallbladder operation on. I took out the gallbladder, and then went in because of abdominal pain, and saw that he had an adhesion formation in this area here near the gallbladder area. So the patient originally didn't have any adhesions at this site, but at the second operation had adhesions at an operative site called 1B.

Type 2A and type 2B, the same kind of thing, no operative procedure at the site of adhesion formation, but this is actually re-operations in that area. In type 2B, operative procedure performed at the site of adhesion, reformation besides adhesion analysis. This pretty much

depicts that particular type there.

This is a patient that I had gone back in on I believe, and had latched some adhesions. Then when I went back in the second time, they had adhesions reform right into that same area. That is type 2A, and that is the most common type of operation as a laparoscopic surgeon that I do. Patients continually come in to see me for abdominal pain, and they have had laparoscopic latching of adhesions before. I go on in and they have adhesions reformed in that same area, type 2A.

Type 2B is where they have had an operation at that site, and you go in there again and the adhesions have reformed at that operative site.

So I reviewed the mounds of material that they sent me, and it took me quite a while to do it, because I'm not that good of a reader in the first. I don't like to read that much. The two questions that I came out with when I reviewed that material were these questions here, and I'm pretty sure there will be more questions as we begin to talk about it.

The two things that I really wanted to find out from the sponsor -- and one of these is sort of my anecdotal case and I will tell you about it in just a second -- is

number one, is there, and if not, should there be any data to show that the safety and/or efficacy of the use of separate coded following pelvic or abdominal radiation?

Now most of you know that in the 1990s we're becoming more and more oriented to doing things pre-operatively before we operate on patients. In other words, we are more and more pre-operatively radiating patients for disease processes. For instance, we'll give pre-operative radiation to a patient with a prostate tumor. We'll give pre-operative radiation to a patient who has a cervical cancer. We'll give pre-operative radiation to a patient who has a rectal cancer, and other problems.

If this product isn't labeled right, then surgeons may think that it's okay to put this product in the pelvis after they have had their pre-operative radiation. I'm not sure -- and maybe you all know this from the sponsor's point of view -- I'm not sure if we have any data that suggests that this is actually safe to do, and whether there is any interaction between that tissue that has been irradiated and the product, the hyaluronic acid that we put in that area.

The problem I had is that since our last meeting when we talked about Seprafilm, I have actually used seprafilm. I had a patient who had a rectal cancer. She

was a very thin patient. She weighed about 130 pounds. She had a rectal cancer. I did a low anterior anesmosis(?) on the patient. She had pre-operative radiation.

She had a very nice, pristine, clean abdomen. Her tissues weren't that swollen. After the operation, which went smoothly -- it took about an hour and a half to do -- I put the piece of seprafilm down there very meticulously down into the pelvic cavity.

Well post-operatively about two weeks later she developed an obstruction; not a small bowel obstruction, but a very significant colon obstruction, and a not a very nice osmosis; above her osmosis. Now that is to me, an anecdotal case, so it doesn't really mean a whole lot, but in my own mind I didn't have any contraindications to putting this product down into the pelvis, and maybe I should have.

I don't know whether that was actually caused by the product. I don't know whether she had an abnormal adhesive response. I do know that she had prolonged morbid operation the second time around and has a colostomy now. I hope to be able to close it in a few weeks. That question still lingers in my mind, and I would really love somebody to answer that question for me later on.

The second is when I reviewed material, again that

I got, I wanted them to please explain the comment made in reference to question 3. So for those of you who don't have the data in front of you, this is what question 3 says, that Dr. Berkowitz I believe, raised. The original success criterion proposed by Genzyme for the effectiveness of the device was a reduction from 30 percent down to 10 percent. Those were the original expectations, in the mean percentage of anatomical sites with post-surgical adhesions.

Have the results demonstrated that Sepracoat reduced the mean percentage of anatomical sites of adhesions from 30 percent only to 24 percent. With 23 anatomical sites evaluated in this trial, a 30 percent incidence translates into 6.9 adhesion sites and a 24 percent incidence translates in 5.5 adhesive sites. Please provide the information supporting the clinical significance of reducing the average number of anatomical sites with adhesions from 6.9 to 5.5.

The answer that I saw in the material that I got was this answer from the sponsor. The answer is, "What is known and documented experiences found in published literature is that even one adhesive band may impair fertility, may restrict the normal movement of an organ causing pain. It may act as a fulcrum from which the

intestines may become entangled, and adhere intestines to the abdominal wall, thereby raising the risk of entering during re-operation. We therefore feel that any reduction in adhesions, even the elimination of just one site, is of clinical benefit."

Now I need to get some more understanding about this, because I'm not really clear about this last statement. That is not a very, very scientific statement to me, "Any reduction in adhesions, even elimination of just one site is of clinical benefit."

I really need to see some more data to substantiate that that is a true statement, because looking at it from the way that I look at it as a general surgeon, if I'm going to do 100 laparotomies here in 1997, I know that 90 percent of those patients are going to have adhesions post-operatively. We know that.

We also know from the literature review and the international literature review that 70 percent of those patients of that 100 patients are going to do just fine over their lifetime, without any further intervention at all. We do know that 30 percent of those patients, or 30 patients are destined over their lifetime, to have some kind of ongoing problem, such an obstruction, acute pain or

infertility. So we're more interested as surgeons in this 30 percent of the patients.

Now as a surgeon what I'm going to do if this product is approved, is I'm going to give Sepracoat to all 100 patients. I know that I'm giving it to 70 patients that it's not going to do any good, but if I am going to significantly impact these 30 patients, I am very interested in the product.

So out of those 30 patients that are destined to have some sort of complication, the question is, does Sepracoat in the study that I saw, does Sepracoat reduce the number of de novo adhesions by 1 out of 7 of the sites of adhesions, which is 14 percent?

Now to me, you can look at that several ways. I originally looked at that, okay is that 14 percent times 30 means that I'm going to help 4.2 patients? No. That was I reduced 1 adhesive site out of 7. That means that those other 6 adhesive sites have just as much clinical significance as that one.

So in actual reality, those 30 patients were destined to have some complications, even with the addition of Sepracoat. Thirty patients over their lifetime still may have some complication of obstruction, pain and infertility.

So this reduction by 14 percent doesn't mean a whole lot to me.

So my question is, does this 14 percent reduction in the number of adhesions or adhesive sites clinically benefit any of these 30 patients, and how are we going to find that data? This is the quandary that I have come to. This is a question that I would really like to have some more in depth discussion on, because to me, we are actually talking about a very, very minuscule number of patients.

Now if we are talking about all of these patients going on to develop gangrene of the bowel, then maybe that amount of reduction, whatever that amount of reduction is, is significant, but not all of these patients are going to have several complications.

If I am going to use this particular product on 100 patients, then I want to really, really know how much clinical benefit that I'm going to have.

So my conclusion is this, that we won't know whether or not such a reduction of adhesions as accomplished by Sepracoat will obtain clinical significance until a post-record study is done. Then and only then will we know whether such a product reduces the complications such as small bowel obstruction, infertility and pain.

Thank you.

DR. MORROW: Thank you, Dr. Duncan.

Your second question is the subject of one of the FDA's questions to the panel, and we will discuss that in some detail after we hear from Dr. Levy.

At this time, could I just ask the sponsor to respond directly to the specific question of is there any experience with this product in patients who have received abdominal irradiation?

DR. BURNS: No, we have no experience with that.

DR. MORROW: Thank you.

The next FDA panel review has been provided by Barbara Levy.

DR. LEVY: I don't have any slides, because we all have to stay awake this afternoon, so we'll keep the lights on. I will keep my comments fairly brief, because we have already had a fairly in depth review.

I wanted to present some comments from the gynecologic viewpoint, which is a little bit different than the general surgery standpoint on these issues. I think it is of significance that all of the comments and papers that we heard about this morning were related to general surgery and the general surgical procedures for the most part, yet

this particular product and this study design was all in gynecologic surgery.

Whereas the complications of small bowel surgery and ileocecal surgery are significant, we don't seem to see the same incidence of post-operative obstruction in the major sequelae of adhesions, at least with respect to obstruction in gynecologic surgery.

I would just ask the sponsor if they could make some analogy for us between those overall complication in surgery in general, and divide that out into surgical procedures for infertility and GYN, versus those in general surgery, because I am concerned that there may be some real differences there that we are not looking at.

I think that we have to address the clinical endpoint, and I think that is something that we have struggled with throughout several panel discussions on adhesion prevention devices, and whether the number of adhesions is an adequate surrogate for a clinical endpoint, which is either infertility or reduction in infertility, reduction in pain, or reduction in obstruction.

I think that is a discussion that we are going to have to have around the panel, but it is at least clear to me that reducing the number of adhesions may not translate

into some clinically meaningful information for us.

The next point I wanted to bring up is are all adhesions created equal? It seems to me that we are really talking about a very specific subset of adhesions in this particular product. All of the data that we looked at tell us about the complications of adhesions in general. The 30 percent complication rate is related to all adhesions, not de novo adhesions.

I think that question was raised this morning, but if we only reduce de novo adhesions, are we reducing complications at all? I think that is a real key point for us to address this afternoon.

The final thing in looking at gynecology and specifics in this particular study, and the particular protocol was that there were more pre-existing adhesions in the controls than in the treated patients, therefore there were differences in pre-existing pathology in these study groups.

My question for which I don't have a clinical answer is did that difference in underlying pathology change the characteristics of the patients and the way that they will respond to surgery a second time? I don't have an answer to that, but I think it raises an issue with respect

to adhesions and whether these patients are more prone to adhesions by virtue of pre-existing pathology. That is something I would like the sponsor to address, and something I think we on the panel need to talk about.

So I think there are some significant questions and issues that we have to address:

1. The relevance of a gynecologic model and study with respect to general surgery, and whether we can just take a GYN protocol and give labeling indications for GYN and general surgery;

2. Whether our surgical procedures are equivalent;

3. Whether the propensity for significant and life threatening adhesions are the same in these populations of patients; and

4. Whether the sponsor has really talked to us about clinical effectiveness in terms that we can translate into something that benefits our patients.

Agenda Item: Review of FDA Questions

DR. MORROW: Thank you, Dr. Levy.

At this point in time the panel has before it a series of questions posed by FDA for our discussion. This is also the opportunity, having now heard presentations both

from the sponsor and from FDA, if there are any unresolved issues in your mind that you would like to ask questions of any of the presenters so far today before we begin to address the questions that are on the table.

DR. DESHMUKH: I had question or a comment. Dr. Berkowitz in the reports said that in baboons the 10 percent of the blood volume, the bleeding time was prolonged, but not with 5 percent blood volume displaced with this solution. Perhaps the human physiology might be different though they are both primates.

What I want to know is that should this device be approved, would the manufacturer have to put a label saying don't use it, or use a cell saver, because you use a cell saver like in aortic surgery where the blood is really viscous, then there is a real possibility of this getting into the bloodstream. That is my question.

DR. BURNS: Was that a question to the sponsor to address, or for the FDA? Well, based on our animal studies, both in the baboon, as well as looking at the clearance rate of the product, and I think Dr. Berkowitz kind of addressed this, that the level of HA that you could potentially get circulating in normal use would be actually quite low, and that would never achieve even the 5 percent level in which

we didn't see any increase in bleeding times.

We also in animal studies did some work with not quite looking at the question that you looked at for cell savers, but we actually looked at putting animals on by-pass, and then actually infusing HA into the by-pass machine, and then back into the animal, and we saw no coagulopathies in that case, mainly because the amount of material that we were using would be significantly less than 10 percent of the blood line.

For normal use of this product, it would be very difficult I think to achieve that level of circulating HA, even if it was to be used in a cell saver, or it might present a problem.

DR. HOROWYJ: I guess the maximum amount is one liter?

DR. BURNS: Well, one liter is the maximum amount used interoperatively, but remember that the product is not left behind. So that actually it is a very small amount of material that would be left in the perinatal cavity.

DR. HOROWYJ: I think Dr. Deshmukh was concerned about using something that recirculates --

DR. WITTEN: Roxy, I think we will let the panel ask the questions.

DR. DESHMUKH: She had the question for me, because 10 percent of that volume would be about 600 cc.

DR. BURNS: Correct.

DR. DESHMUKH: If you are you in the cell saver use continuously, then you are using it in real surgery for instance.

DR. BURNS: It is an interesting point, because the way that we have the directions for use of the product is to administer a certain amount, and then remove the excess. So I'm not sure whether we would ever have 500 or 600 mls ever in perinatal cavity at one time. It's a good question. It's something that we should look at separately.

DR. DESHMUKH: I think you should look at that.

DR. MORROW: I think we have heard the data that is available on that particular issue, and any further recommendations can be based on the panel's ultimate decision.

DR. BURNS: Dr. Morrow, would it be possible for us to clarify some of the issues that were brought up by the FDA before break at lunch? Spend maybe five minutes addressing a couple of clinical issues, as well as some statistical issues.

DR. MORROW: Why don't we start with our

questions, because some of them bear on those, and then as we go along you can address those points as we are going through them.

If we could have the questions up please. The first question before the panel relates to the fact that the control group had statistically more -- 4.5 versus 3.2 -- pre-treatment adhesions. Is this difference in patient characteristics clinically significant to the assessment of the 4 percent Sepracoat solution's effectiveness?

I need to poll the various members of the panel regarding their opinions on this, so we will start with Dr. Downs.

DR. DOWNS: The thing about this that I would be concerned with would be the possibility of a graduate shift in definitions or in procedures over the course of the study such that perhaps adhesions are less frequently defined or discerned in the latter part of the study, in which case it would bias the results in favor of the device.

DR. MORROW: So I gather then that your opinion is that this may in fact represent something that will influence the results?

DR. DOWNS: Absolutely.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: I agree. I think it's significant that you are not starting on level ground. You need to start on level ground in order to effectively compare the two, and show if there is a significant increase in pre-treatment adhesions already there. Then I think it would impact upon the end result of post-operative adhesions formation observation.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: Yes, I think Dr. Levy noted that it may indicate that patients who are in the PVS group may have a greater tendency to form adhesions. So it may potentially be clinically relevant.

DR. MORROW: Dr. Levy, I think we heard your thoughts on this matter a second ago. Do you have anything else to add?

DR. LEVY: No. I agree that it makes a difference.

DR. MORROW: Dr. Deshmukh?

DR. DESHMUKH: I think that it makes a difference in the operative duration. The fact that the control group had more adhesions may suggest that they have a greater tendency to form adhesions, so therefore the study showed that there less adhesions with Sepracoat, then this

difference should pirouette the use of Sepracoat rather than against it.

DR. MORROW: Would other panel members like to respond to that?

DR. AZZIZ: I think I know where Dr. Deshmukh is coming from, but actually it is the opposite I think. If the control PVS has a higher adhesion score to begin with, which means they may have more adhesion forming potential, then they would tend to have more adhesions at the end of the study, which would nullify, or actually increase the difference between the control and Sepracoat, as opposed to decrease it. So I think not. That reasoning is probably not correct.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I think if you had a very large percentage reduction in the number of adhesions with Sepracoat, then a small difference in the initial adhesions would not make as much difference, but the smaller your reduction of adhesions by this product the more important and more significant your initial differences become. So I do think it is very important.

DR. MORROW: Ms. Domecus?

MS. DOMECUS: I don't know if I have an answer,

but I would like to make a point. I have heard earlier today some skepticism expressed by the panel about the clinical relevance of the difference of approximately one adhesion in terms of the effectiveness results. So if you think that is not clinically meaningful, I don't know how we can answer this question, where there is about a difference in one adhesion, and say it is clinically meaningful. There just seems to be a disconnect in those different viewpoints, if I am understanding the data correctly.

DR. MORROW: Dr. Dorfman?

DR. DORFMAN: Yes.

DR. MORROW: Is there any further discussion on the panel's part on this particular point? Was one of your responses specifically related to this question?

DR. BURNS: Yes, it was, Dr. Morrow.

DR. MORROW: In one minute or less, fire away.

DR. BURNS: Dr. Diamond will respond.

DR. DIAMOND: I think there are a couple of important points to keep in mind here. First of all, with having more pre-existing adhesions in the control group, there is actually more potential sites at which de novo adhesions could form in the Sepracoat group. So I think that's a bias against it, number one.

Number two, given the data that has been presented, that was in fact observed, if you do co-variate analysis to control for that difference in the initial adhesions, what I presented before and what you see again before you now is the adjusted mean proportions of 0.26 in the control group, 0.20 in the Sepracoat group, which still remains statistically significant. So even controlling statistically for this difference makes it significant.

Finally, if you look at this last overhead here, which is actually very similar to the one that was presented by the FDA clinical review, this is looking at the number of baseline adhesions on the X axis. What the Y axis is looking at is a number of sites of de novo adhesions observed in the tomasecula(?) procedure.

What you can see from this is that what all of you have been saying is that since they have more adhesions at issue, they are more likely to form adhesions. In fact, what you can see here is if anything, it's exactly the opposite. The patients that had the more adhesions to begin with are not the ones who had the more sites that were involved with adhesions.

Even if you compare for example patients with one and two and three sites initially, with those with six,

seven and eight sites with adhesions, so that each of them have lots of sites available for de novo adhesion formation, you see if anything you had more de novo adhesions developing in the patients who had the fewest to begin with. If you look at the regression line there, it gets close to flat. This is for de novo adhesion formation.

We previously published back in 1987, a very similar comparison looking at the incidence of adhesion reformation as a function of how many adhesions are present at the time of the procedure. What we saw at that time was a curve that was even flatter than what you see here.

So in fact there is not any evidence either from our current work, or from the study database, which is 40 now, which is to show that the patients who have had the most adhesions initially, have the greater propensity to form de novo adhesions.

DR. MORROW: Thank you.

Is there any further discussion on the part of the panel on this question? Is it a fair statement to say that as I hear the panel's responses, that they remain concerned due to the relatively small differences in effectiveness demonstrated in this study, that this small difference may represent some degree of biologic diversity? Is that the

sense of these remarks?

Dr. Witten, does that respond to the FDA's question?

DR. WITTEN: Yes.

DR. MORROW: Could we have the next question please? The next question relates to adverse events. In the critical study, it was noted that there was a statistically significant difference in the incidence of abdominal pain, nausea, dizziness and pharyngitis among the patients receiving the product when compared to the control group. You have seen the data of the physicians on the long-term sequelae. What is the feeling of the panel in terms of safety concerns regarding this product? Are these differences clinically significant?

Dr. Dorfman?

DR. DORFMAN: Maybe.

MS. DOMECUS: I don't believe they are.

DR. GALANDIUK: Yes.

DR. DESHMUKH: No.

DR. MORROW: Could you elaborate please?

DR. DESHMUKH: I believe that the benefit has been shown by the studies is more significant, and therefore I, the physician, will be willing to subject my patients to

increased discomfort post-operative for the benefit.

DR. MORROW: If we ignore the question of risk/benefit and just focus on the question of risk, which I believe is what we are being asked to assess here, do you believe these data suggest that there is significant clinical risk of adverse events?

DR. DESHMUKH: No.

DR. MORROW: Dr. Levy?

DR. LEVY: I agree with the sponsor. I think that these adverse events are common to the types of procedures that were being done, and are not related to the device.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: I have to hedge and say maybe, which is not very scientific, but the answer is maybe.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: I think that the events of pain, nausea, dizziness and pharyngitis are relatively small, and I don't think that they would have any great impact on the use of the product. I don't think the symptoms are that extreme that they would warrant any concern.

DR. MORROW: Dr. Downs?

DR. DOWNS: When I look at Table 37, comparing the 0.4 percent of high viscosity HP with PVS, the 3 most common

side effects are statistically higher in the treated group, with a percent difference of 15 percent or so. The first top 10 side effects, 9 of those are higher in the treated group than in the controls. It looks like a pattern to me, and I just can't believe it's all due to chance.

DR. MORROW: Further discussion of this issue from those people who did not feel these results were of clinical significance?

DR. GALANDIUK: Many of these are so non-specific in terms of abdominal surgery that I don't know if you can -- with the fairly low incidence they have, I don't feel comfortable in saying for sure that's related to the Sepracoat.

DR. LEVY: My level of comfort was related to the fact that there were no sequelae. That these were transient symptoms that are symptoms that are common with abdominal surgery. They can be related to tissue trauma and other issue. They have been related to time of surgery and other things that were not quantified for us.

In terms of safety, these are not issues that impact long-term sequelae for patients.

DR. MORROW: Dr. Witten, I think you have the clinical sense of the panel that this is not a major

clinical issue relative to safety.

Next question. Further safety issues related to serious adverse events. The question has been raised that possibly one patient with a history of smoking and asthma developed pneumonia, which progressed to ARDS after this surgery. There was one patient who developed a wound hematoma on post-operative day nine. These were graded as serious adverse events.

Are these events felt to be significant in the assessment of the safety of this product?

Dr. Downs?

DR. DOWNS: I did a pi square, and the two sided p value is 7 percent, with 12 serious events in the treated and 4 in the control. It is not statistically significant.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: I'm not a statistician, but the basic numbers that are up there, I don't think that is clinically significant in the assessment of safety.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: No.

DR. LEVY: I would be a little bit concerned about the one patient with the pulmonary infusion and the ARDS with respect to the pulmonary excretion of the CO_2, and

whether that may have been related in some way. From the information that we have, it doesn't seem like it would be, but it is something I would want to go back and look at, and just see if this was a patient who might have had some COPD, that the increase in PCO_2 may have been in some way related to her complication.

DR. DESHMUKH: I don't think that it is any problem.

DR. GALANDIUK: I agree with Dr. Levy.

MS. DOMECUS: No.

DR. DORFMAN: No.

DR. MORROW: Thank you. I think that the feeling is that there is not any demonstration of significant adverse risk associated with this product.

Now I think we come to the question that Dr. Duncan raised during his presentation, as did Dr. Levy, namely that the mean proportion of patients with de novo adhesions in the treated group was 88.8 percent, compared to 95.4 percent in the control group. Is this level of reduction in patients with de novo adhesions clinically significant to the assessment of this product's effectiveness?

This being a somewhat more difficult question, Dr.

Dorfman?

DR. DORFMAN: Maybe.

MS. DOMECUS: Although again, not directly related, I think that our answer to question 1 was yes; the answer to this question should also be yes.

DR. MORROW: Dr. Galandiuk?

DR. GALANDIUK: I don't think this reduction is clinically significant.

DR. DESHMUKH: I agree with her. That is not significant.

DR. LEVY: I agree. I do not think that this is a clinically significant change in number of adhesions.

DR. AZZIZ: I have to agree, probably not significant.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: Likewise.

DR. DOWNS: Me too.

DR. MORROW: May I then ask the panel what would demonstrate to them that this was a clinically significant benefit? What sort of outcome measures would you need to see?

DR. GALANDIUK: I think it would be good to have follow-up data on number of destructive episodes. It would

be nice if you could have a surgery, as Dr. Beart described earlier today, which has a fairly high incidence of actually admission for obstruction, clinically significant episodes of obstruction. You would love to see a greater percentage in reduction of adhesions of 10 percent or more.

DR. AZZIZ: Obviously to calculate any kind of size and significance, it is almost really a guesstimate, but if you take that your controls have 95 percent adhesion formation, you really would like to see at least a 20 percent reduction in adhesions before you consider that clinically relevant. I think a 5 percent or a 3 percent or a 6 percent is probably not going to do that.

So I would say my recommendation is to see a 15-20 percent reduction from that of controls.

DR. LEVY: I have several issues, some of which are real world issues, and some of which aren't. The question that I raised before is whether de novo adhesions are the ones we need to be worried about at all, or whether adhesions related to direct tissue trauma are more significant.

That may be a basic science question rather than a clinical question, but it is something that came to mind for me throughout the evaluation of this PMA, which is that it

is that it is not clear to me, especially since in this particular case the abdominal wall site was wiped as a site of de novo adhesions since it was involved in direct surgical trauma for all cases. I would just like to see an analysis of whether de novo adhesions are the ones we need to be worried about at all.

DR. MORROW: Dr. Dorfman, you had a comment?

DR. DORFMAN: Yes, to me the most clinically relevant issues could not be addressed by the material presented to us. If there is an adhesion at a tubal ovarian site that causes infertility, that is clinically relevant. If there is a subsequent bowel obstruction, that is clinically relevant. Where it is, is a very important issue with regards to clinical relevance.

DR. LEVY: I think the outcome measures that would tell me clinical effectiveness are either infertility, a difference in pain, or a difference in obstruction.

DR. AZZIZ: I have to agree. We are looking -- and I think Dr. Levy brought this up earlier -- we are looking at a model that is gynecologic. The incidence of bowel obstruction from de novo adhesions in gynecologic surgery is certainly unknown, but it will certainly be less than the 1 percent that Dr. Ellis presented earlier with

general abdominal surgery.

So I think we are talking about something that is extremely rare to begin with, according at least to the specifications that the sponsor wants to bring, so that we should be able to see some change that would be significant for the product to be useful.

DR. DUNCAN: I agree. I think that we have no idea of the amount of the problem that we are talking about, and the amount of problem that de novo adhesions actually presents clinically is again unknown, but even if you knew that de novo adhesions presented with a major problem, you would like to see a more clinically significant reduction in those de novo adhesions, but not knowing for what kind of clinical endpoint you are going to get, a small reduction like that to me is still not clinically significant.

DR. MORROW: Do you have a comment?

DR. BURNS: Thank you, Dr. Morrow. You are very kind.

Just a couple of quick comments. We agree with the discussion that adhesion prevention is not saying that there is going to be an improvement in any sort of clinical outcome. Obviously, those are studies for the future. I think it has been established, at least in prior meetings

that adhesion reduction in and of itself is a valid clinical outcome.

The question about adhesion reduction in a GYN procedure and how that would translate to some sort of effectiveness in abdominal procedure and vice versa, let me say that this GYN study was a model to look at whether if one prevent tissue damage intraoperatively, can one prevent adhesions. It wasn't to try to ask these other questions.

Additionally, we do have some information about surgeons' impressions through a survey on the level of effectiveness in terms of adhesion prevention as a potential clinical outcome. I don't know if it is appropriate if we can present that at this time, but we do have a survey.

DR. WITTEN: I don't think this is the right time to present it. That is material that hasn't been reviewed, isn't that right?

DR. BURNS: The initial survey was?

DR. WITTEN: Oh, it was part of the PMA? Then you can present it from our point of view.

DR. DIAMOND: We have put together what is now a series of four different abstracts, which have been presented at different meetings such as AAGL, ISGE and others. What these have looked at is surgeons' opinions or

impressions of what extension of reduction in adhesions would be important for issues relating to number one, pelvic pain, and number two, with regard to pregnancy outcome.

What we did basically is bring a series of 126 different scenarios, amount of adhesions and then locations of those adhesions; that is, what structures were involved. We then asked them how likely do you think this person is to conceive in this situation? We controlled for all the other factors in infertility.

That is why the clinical trials and the clinical outcomes we would like to have are so hard to do, because of all the confounding variables. We said, if we control for these and all the other fertility factors, the only issue is adhesions on the pelvis, what is going to be the likely contribution of adhesions to pregnancy outcomes?

For example, one of the things we looked at was if we had adhesions to both ovaries and both tubes, and we said it involved 90 percent of each of these organs, 80 percent of each of these organs, all the way down to 5 percent of each of these organs. We ended up with pretty much of a straight line relationship between the two such that if you did the appropriate analysis, for any reduction of adhesions that you achieve, you would see an increase in the pregnancy

outcome, if you just compare one point on the graph with a subsequent point on the graph.

DR. LEVY: Could I ask you a question about your methodology? This was based on a survey of people's opinions or actual data on patients?

DR. DIAMOND: Again, there is no data. That is the problem. This is surgeons' opinions, because there is no data where you are going to be able to control for the husband's sperm count and the wife's ovulatory status, and endometrial biopsy and whether that is in phase, and all those other conditions. So that we don't have any kind of clinical data like that, and odds are we will never have that level of data. That is was an opinion study.

We had the same sort of observations looking at the issues with regard to pain. While it didn't have as steep a curve, it again showed that to the extent that you could -- going by the physicians' opinions -- to the extent that you could reduce adhesions, it was their consensus that you would reduce the amount of pain that was present.

DR. MORROW: Thank you.

DR. AZZIZ: Michael, were you addressing the issue of how much is enough as a change? I'm confused about the anecdotal study there.

DR. DIAMOND: The question is how much of a reduction is clinically significant?

DR. AZZIZ: But you said that it was a straight line, which means that there was really no break point. In other words, if you had said to me we are going to do a survey of 1,000 surgeons and say, this is just an opinion, but 1,000 surgeons, and most of them clustered around 25 percent, then we can say 25 percent, but this is a straight line. So in fact you are supporting the fact that there is no suggested change in amount of adhesions. Is that right?

DR. DIAMOND: No, what I would say it suggests is that there is no one point where all the sudden adhesions cause infertility. I think the more adhesions that you have --

DR. AZZIZ: But your study can't say that. That was just purely anecdote. I mean you were asking people's opinion as to what they thought was a significant amount of adhesions. Your study showed that in fact there is no such standard, that it is linear. Some people think a little bit, some people think a lot.

DR. DIAMOND: No, what it was again was we gave them 126 different scenarios. So we said if you had 90 percent adhesions, 80 percent adhesions, 70 percent

adhesions. We said what do you think is the likelihood this person would conceive, or that this person would have pain? We got the responses from each of the surgeons, and then we summarized them.

So we were not asking at what point would this cause infertility. We said, how likely is it?

DR. AZZIZ: Is that valid scientifically, that methodology of assessment success?

DR. DIAMOND: It is an opinion, just that.

DR. GALANDIUK: I think we all realize how hard it is to do a study looking at adhesions, and I don't think anybody disagrees with that. I think it is just if you have a relatively small difference in number between groups, more supporting data could be obtained by clinical results saying well, there was only less adhesion, but these patients had less hospitalizations for obstruction or a greater pregnancy rate, or just something else to bolster the support.

DR. DIAMOND: Unfortunately, you have, as Dr. Levy was talking about, the logistics. If you have even Dr. Ellis' incidence of 1 in 100 patients, 1 percent incidence, in order to see a statistically significant difference of any one intervention, you have to have a huge number. That assumes that there are no other inter-current events over

the time course that would impact upon that.

DR. MORROW: Thank you. Is there further discussion from the panel on this topic?

Dr. Witten, I think it is the sense of the panel that given the relatively small differences between the treatment and the control group here, it is not possible to say that this clearly demonstrates effectiveness for the secondary endpoint of de novo adhesion formation, demonstrates clinical effectiveness given the differences that are being observed.

Do we have more questions?

This relates to the mean proportion of available sites, rather than the percentage of patients, which I believe is what we just discussed. So the mean percentage of available sites with de novo adhesions per patients for the treatment group was 23.6; for the control group, 29.5. Is this reduction of de novo adhesions clinically significant in terms of effectiveness?

We'll go from this end of the table. Dr. Downs?

DR. DOWNS: I will pass on that.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: It just doesn't look to me like those numbers are that significantly different, and it would be

hard for me to imagine that this reduction of de novo adhesions will provide any clinical help to the patients.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: I have to agree with Dr. Duncan.

DR. LEVY: I agree. The difference in 0.7 adhesions is not significant.

DR. DESHMUKH: Not significant.

DR. GALANDIUK: Not clinically significant.

MS. DOMECUS: Again, in answer to question number one we said that a difference of about one adhesion per treatment was clinically relevant, so I don't know how we can say something different in answer to this question.

DR. DORFMAN: Not clinically significant.

DR. MORROW: I think that you have the same issue of magnitude of effect here as far as clinical relevance, that we discussed on the previous question.

Further questions?

This is related to an issue that we have already talked on, the protocol for the reasons just reiterated by the sponsor, utilize the incidence of de novo adhesions as a surrogate endpoint for long term sequelae and morbidity of adhesions such as chronic abdominal and pelvic pain, infertility, and small bowel obstruction. This surrogate

endpoint has not been validated. What steps should be taken to valid this endpoint to demonstrate the clinical benefit of adhesion reduction is effective in reducing the long-term sequelae or morbidity of adhesions?

I believe unless people have something further to add, that this was addressed during our previous discussion in terms of actually looking at clinical endpoints listed on the slide, and their occurrence in treated and untreated patients.

Yes?

MS. DOMECUS: I believe that when this panel met last year to review the Seprafilm devices, the question was also put to the panel. The panel had decided that the surrogate endpoints were sufficient for approval of the product.

I also want to point out that devices and instruments used for adhesion analysis and other barrier methods that have been approved for prevention of adhesions have not had to look at these clinical outcomes. I don't know why we would single out this device, and the put the burden on them to prove clinical outcomes associated with reduction in adhesions.

I see that it is slightly different in terms of

being a preventive device as opposed to adhesion analysis, but still the aim is to reduce adhesions.

DR. MORROW: I think the sense of the panel as I got from Dr. Azziz's comment, which I think summarized things nicely was that had a larger reduction in incidence been demonstrated, that that would be an analogous situation to what happened last year with the other product, but with this very small difference, I think more questions are raised about clinical significance, and I think that is the panel's issue.

Other discussion of this topic?

DR. WITTEN: I'm just wondering if anyone on the panel wants to comment further on Dr. Levy's question about the relevance of the gynecological model to general surgery procedures? I would be interested if there is any further discussion on that point.

DR. AZZIZ: I, as probably the only other gynecologist here, would like to comment as well. Certainly the gynecological model is totally different than general surgery. Whether we like it or not, it is a totally different organ to operate.

We are concerned with very specific organs, the tubes, the ovaries and the uterus and colosac, and that is

it. If we can't really separate one organ out of another, it is at the bottom of the pelvis. It is in a small, enclosed area. It is the loops of bowel that are generated across the entire abdominal cavity. It isn't bowel surgery, which generally tends to be more contaminated.

So I'm not quite sure -- in fact, I'm pretty sure that you cannot use either general surgery models to apply directly to gynecology and vice versa. They can be used as a basis for originating another study, or as a basis for saying these potentially may be useful, but to apply say tubal ovarian surgery to bowel surgery, is probably not directly related. I would like to obviously hear from the general surgeons.

DR. MORROW: Comments from general surgeons on the panel?

DR. GALANDIUK: It is a model of adhesions, and probably a more easily reproducible model than a general surgical case, where there the size of incision, the amount of resection. This is probably more equivalent of surgery, and therefore easier to study in terms of adhesion, but if you are looking at things like affect on incidence of small bowel obstruction, I don't think you can equate them.

DR. LEVY: I think too a lot of these cases were

infertility surgery, and infertility surgeons tend to use different surgical technique than so-called macro surgery, so that I still have a question with respect to how much packing was really done in these cases. There may be many cases that didn't have packing at all.

The types of technique that are used may be different. Suture material may be different. There are a lot of things here. Many, many of these patients, they all wanted fertility, at least preservation of fertility as an endpoint, so much so that they were willing to undergo a second surgical procedure to help enhance their fertility.

I think that that raises an issue about what kind of surgery was really done here, and whether that is analogous to all abdominal surgery.

DR. AZZIZ: Does that answer your question?

DR. MORROW: Are there any further questions? Any questions from any of the panel members about any of the issues that we have discussed or any other points that you need brought into the discussion prior to voting?

DR. DUNCAN: I'm just curious about one thing. I see the sponsors tried several different types of solutions and several different types of concentrations. I was wondering why a 0.4 solution was used, and what do you think

would happen if they went up to a higher percentage? Would it be more effective then, or is there some increase in adverse effects when you get the solution at a higher concentration?

DR. BURNS: Based on our animal data you can go to higher concentrations or higher viscosities, which is really what is effective here, and probably get some enhanced effect. You actually get some limited returns as you go up into viscosity. Then probably you will start to get into some handling problems. So based on the animal data and also a study that we did looking at handling properties, we felt that the 0.4 percent solution would be the optimum concentration.

DR. GALANDIUK: I have one question. In Europe, where this product has already been released, do you have additional clinical information from those countries?

DR. BURNS: We haven't conducted any formal clinical trials, although we have been in contact with surgeons that are setting up to do some trials in cardiac surgery and some other areas. We know that they are very pleased with using the product in terms of being about to do the surgical procedure without any effect on their ability to do the procedure, but we don't have any formal clinical

trials at this point.

You have to keep in mind it is very difficult to do a trial, especially on abdominal surgery. It is actually probably impossible to look at adhesion reduction with looking at de novo sites. I might actually ask Dr. Beard to comment on that. I can't imagine a study design where you could actually show reduction of de novo adhesions in a general surgical procedure.

Dr. Beard, would you mind?

DR. MORROW: I actually think that Dr. Galandiuk's question was more related to did you have any long-term follow-up on clinical outcome, rather than formation of de novo adhesions.

DR. BURNS: No, we haven't done that.

DR. MORROW: Thank you. Dr. Azziz?

DR. AZZIZ: Along the same lines, is there no randomized European trial?

DR. BURNS: Let me refer that question to our medical group.

DR. MOSCICKI: At the present time, no, we are not conducting a randomized trial, although we would like to eventually look at a combination trial with both Sepracoat and Seprafilm and have been planning such a study to look at

long-term outcomes over a very large group of patients over a very long period of time. This can really only be done in a post-marketing environment, however.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: Dr. Burns, do you have any information on additional time that application of Sepracoat would add to the surgical procedure? It's non-continuous.

DR. BURNS: I don't think it adds significantly to the length of the procedures, but I'm going to have to defer in the answer to that to our clinical group. Do we have that data? Could one of our surgeons make a comment?

DR. BEAVER: Eric Beaver. No significant time. It's literally the time it takes to pour in the 50 to 100 ccs, the time it takes to pour in the initial 250 and suction that back, the 1 minute that you let it stand in the cavity.

DR. AZZIZ: You don't have to cover it, spread it?

DR. BEAVER: No, the application process when we enter peritoneal cavity was to instill 250 ccs of the device, let that sit for a minute and suction it back. Every 30 minutes or as needed, we then would reapply 50 to 100 ccs over those areas, again, suction it back after a minute application. So in the course of a couple hour

procedure, you would do that approximately 4 plus times, and then again at the end of the procedure. So we are talking about a total application time of less than 5-10 for an average laparotomy.

DR. MORROW: Are there any further questions from the panel?

DR. LEVY: I actually have a question for Dr. Lin. I'm not a statistician and I was a little confused by the end of the morning. Perhaps it's the three hour time delay here from East Coast to West Coast.

As I understood your analysis, at the end, once you took a look at the variance among sites, that these differences were not statistically significant? Is that correct? That when you re-analyzed the data?

DR. LIN: I missed the endpoint you were talking about. Which endpoint?

DR. LEVY: If we looked at de novo adhesions. If we looked at number of adhesions, was I correct that when you re-analyzed that, that was not statistically significant when you corrected for that, or was I misunderstanding what you said?

DR. LIN: Are you talking about the number?

DR. LEVY: Yes.

DR. LIN: The number -- not a proportion, the number?

DR. LEVY: Right.

DR. LIN: The number is actually not statistically tested. Remember it is related to the proportion, and the proportion I had problem to assign a P value to it. So I was just showing an estimate of the clinical difference, which was 0.7 adhesion based on the real time surgery.

DR. LEVY: As I understand your analysis, statistically you feel that it is not possible to assign a p value because of the variation across sites?

DR. LIN: Each of them by center interaction, yes, on the proportion.

DR. LEVY: Thank you.

DR. BURNS: Dr. Morrow, that was one of the points that we wanted to clarify.

DR. MORROW: We will hear a final comment from you on the statistical activity.

DR. BURNS: Thank you very much. Dr. Chiacchierini.

DR. MORROW: A final, brief comment.

DR. CHIACCHIERINI: There are three very basic issues in this question. The first one is the interaction

analysis. The interaction analysis is simply a means to detect differences across centers. How interaction is handled is a matter of statistical opinion.

The concern that one has when you have this kind of an approach is that the use of proportions, the proper analysis for the use of proportions -- proportions do not generally meet the appropriate assumptions for analysis of variance. So the company in its statistical plan, used the arc sign transform, which tends to make the proportions more consistent with the analysis of variance assumptions.

I would like to address this issue. There were 16 investigator sites in which there was a difference. Of those, there are 12 for the mean difference that are in the direction of Sepracoat, and there are only 3 that are in the direction of the PVS control. The large site, number 3 -- this difference deals with the proportion.

You will note that the large site, number 12, has a very large proportion, but that was a very small number of patients.

The proportion at site number 3 that we have already discussed, was the source of an interaction effect. Once that site was removed, the interaction effect was removed. In fact, the impact of the device was much more

pronounced. So the inclusion of that site, as the company did in their analysis, did in fact bias against that particular issue.

DR. MORROW: Thank you. Are there any further questions from the panel? Hearing none, our executive secretary, Gail Gantt, will now review the voting instructions for the panel.

MS. GANTT: The voting members of the panel will be asked to formally vote on a recommendation to the FDA on this submission. Dr. Morrow will ask for a motion from the panel. There are three options: approvable, approvable with conditions, or not approvable.

For approvable, if you vote that the PMA is approvable, you are saying that FDA should approve the PMA with no conditions attached.

Approvable with conditions. If you vote for approvable with conditions, you are attaching specific conditions to your recommendation that FDA approve the PMA. The conditions must be specified with a motion for approval with conditions. In other words, you may not vote for approval with conditions, and then determine the conditions.

Examples of approvable conditions are changes in the draft labeling, resolutions of questions concerning some

of the data. Examples of post-approvable conditions are post-market studies and periodic reports.

You propose the extent of the condition of approval such as number of patients, the type of report to be generated if you need a specific report. You must state the reason for this particular condition.

For not approvable, the third option, the exception by this can be Subpart 2, paragraphs A-E state that a PMA must be denied approval for a number of reasons, and I will discuss three relevant reasons. One is the lack of showing of reasonable assurance the device is safe under the conditions of use prescribed, recommended or suggested in the labeling.

Safe means that there is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probably benefits to health from use of the device or its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use outweigh the probable risks. It is a benefit to risk ratio.

The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of a reasonable risk of illness or injury associated

with the use of the device for its intended uses and conditions of the use.

A second reason is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in labeling. Effectiveness can be defined as a reasonable assurance that a device is effective when it can be determined that it will provide clinically significant results.

This determination must be based upon valid scientific evidence that in a significant portion of the target population the use of the device versus intended use and conditions of use when accompanied by adequate directions for us, and warnings against unsafe use will provide clinically significant results.

Finally, the PMA can be recommended for not approval, if based on a fair evaluation of all of the material facts and your discussion, you believe the proposed labeling to be false or misleading.

If you vote for disapproval, FDA asked that you identify the measures that you believe are necessary, or the steps that should be taken to place the application in an approvable form. This may include specifics on additional studies.

The process begins with a motion from a member of the panel. It may be for any of the three options, recommendation for approvable, approvable with conditions, or not approvable. If the motion is seconded, the chair will ask if anyone would like to discuss the motion and so forth.

Please remember that proceedings are taped for later transcription. Nonverbal signals are not captured on tape. If you wish to second, state so, rather than nodding your head please, or waving your hand. Please vote yes, no or abstain.

I would also like to read into the record the appointment of temporary status voting for Dr. Azziz, which I did not read earlier.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter of the Center for Devices and Radiologic Health, dated October 27, 1990, and as amended April 20, 1995, I appoint Ricardo Azziz, M.D., as a voting member of the General Plastic Surgery Devices Panel for the duration of the meeting on May 5, 1997.

For the record, Dr. Azziz is a voting member of the Advisory Committee for Reproductive Health Drugs of the Center for Drug Evaluation and Research. He is a special

government employee who has undergone the customary conflict of interest review, and has reviewed the material to be considered at this meeting.

This is signed by Dr. Michael Freedman, lead deputy commission for the Food and Drug Administration.

A major vote carries the motion, and the voting members for today's portion of the meeting: Dr. Titus Duncan; Dr. Barbara Levy; Dr. Ricardo Azziz; Dr. Narayan Deshmukh; Dr. Thomas Downs; Dr. Susan Galandiuk. Dr. Morrow as acting chairperson, only votes in the case of a tie.

DR. MORROW: Is there a motion from the panel?

MS. GANTT: It is customary for usually the primary reviewer to initiate the motion, though any member of the panel can initiate a motion.

DR. MORROW: Do either of our primary reviewers, Dr. Levy, Dr. Duncan have a motion?

DR. LEVY: Okay, I'll start. I move that we find the device not approvable due to lack of scientific evidence that it is clinically effective.

DR. MORROW: Is there a second?

DR. DESHMUKH: I second the motion.

DR. MORROW: Is there discussion on the motion? Okay, in that case will all those in favor of the motion

raise their hand? Dr. Galandiuk, Dr. Deshmukh, Dr. Levy, Dr. Azziz, Dr. Duncan, Dr. Downs.

All opposed? No one.

[Whereupon the panel unanimously voted for not approval.]

In that case, the recommendation of the panel is that the pre-market approval application for Sepracoat from Genzyme Corporation be recommended for not approval.

Now we need to poll the members of the panel on their recommendations for measures which would place this application in an approval category. First, would you please state your reasons for voting the way you did.

Dr. Galandiuk.

DR. GALANDIUK: A small question of clinical efficacy, coupled with the number, and some question as to how the study was conducted at different sites.

DR. MORROW: Dr. Deshmukh?

DR. DESHMUKH: I believe that no exhibition defense was shown between the control and the study.

DR. MORROW: Dr. Levy?

DR. LEVY: I think I have already stated my reasons.

DR. MORROW: Dr. Azziz?

DR. AZZIZ: A small difference for an entity that we are unclear is significant at that.

DR. MORROW: Dr. Duncan?

DR. DUNCAN: Again, the same thing. I think it's a very, very small difference as far as efficacy is concerned, and I would like to see a larger effect.

DR. MORROW: Dr. Downs?

DR. DOWNS: I also think that the difference is small, and I'm not sure that the evidence even supports that difference.

DR. MORROW: Thank you. Now we would like to have discussion of measures which you feel the sponsor could undertake to place this application in an approval form.

Dr. Azziz.

DR. AZZIZ: Two things. The sponsor is using a gynecologic model because it is readily accessible to a second look laparoscopy, because these patients are much more amendable to it rather than abdominal surgery, however, the downside of gynecologic models is that they do not have the same rate of complications from de novo adhesions as the sponsor would like to look at as compared to patients with abdominal surgery.

So one could construct and should construct a

follow-up study of at least one year, maybe more, in abdominal surgery patients without the need for a second look laparoscopy, and simply looking at the primary endpoint, which is abdominal pain, recurrence and bowel obstruction. If the incidence is somewhere between 1 and 2 percent, there should be enough numbers of patients to define the difference.

DR. MORROW: Other comments on the studies which might be undertaken? Dr. Galandiuk?

DR. GALANDIUK: You might consider a study as was done for Seprafilm, in that group of patients that are going repeat operations to close their ileostomy. It also might consider including either a fewer number of centers, or a somehow more homogeneous mix of performing study at different centers, so that intersite variation wouldn't be a problem.

DR. MORROW: Other comments from the panel?

DR. LEVY: I would really like to see some standardization in surgical technique as well. This was a vast array of surgical procedures, and a large number of study locations. It made it very difficult to assess what was really going on with these patients, and the effectiveness of the device, versus the differences among

patients. I found that extremely difficult and hard to sort out all of that data. I would ask the sponsor to strive for a more homogeneous surgical procedures, homogeneous technique, and small number of sites if possible.

DR. MORROW: Certainly a homogeneous patient population is a possibility. Do you believe that it is realistically feasible to ask for standardization of surgical techniques?

DR. LEVY: It's not the techniques specifically, but for example packing versus not packing. In an infertility population of patients, there may be a large number of us who do not use laparotomy packing at all in our surgical procedures, which would change in large measure the risk of de novo adhesions if we've got no cotton, no fibers in there at all.

So at least with respect to packing or not packing, using a self-containing retractor or not, those kinds of things. Certainly we can't standardize for type of suture material or no resurgence, that kind of thing.

DR. MORROW: Further discussion from the panel?

DR. DESHMUKH: I have a suggestion for the manufacturer that they could consider patients have a temporary colostomy, because many of them, you have a chance

to go back in and close them, and they could study that.

DR. MORROW: Thank you.

At this point we will have a brief break while the room is cleared, and meet again in closed session as soon as that happens.

[Whereupon the meeting was adjourned at 2:36 p.m., to reconvene at 2:45 p.m. in closed session.]